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(54) VARIANT NUCLEOSIDE-5'-PHOSPHATE-PRODUCTIVE ENZYME

(57)Abstract:

PROBLEM TO BE SOLVED: To provide a new variant nucleoside-5'-phosphate-productive enzyme improved in nucleoside-5'-phosphate productivity, to provide a new means for obtaining the enzyme, and to provide uses of the above enzyme.

SOLUTION: This variant nucleoside-5'-phosphate-productive enzyme has such characteristics that there are one Lys residue, two Arg residues and two His residues, the C $\alpha$ -C $\alpha$  distances therebetween stand within a specific range, respectively, there is a space to which a nucleoside is bound in the proximity thereto, there have phosphate group transfer activity and/or phosphatase activity, and thereby nucleoside-5'-phosphate productivity is improved. A method for producing this enzyme by determining a variation based on the X-ray crystal structural analysis of the corresponding well-known enzyme is provided. By this method, the objective enzyme of higher activity can be easily obtained.

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CLAIMS

[Claim(s)]

[Claim 1]In a nucleoside 5'-phosphoric acid production enzyme, one Lys residue, two Arg residue, Two His residue exists and there is distance between such Calpha within limits shown in drawing 1, And a variant nucleoside 5'-phosphoric acid production enzyme whose nucleoside 5'-phosphoric acid productivity of an enzyme which has a space which a nucleoside combines near the, and which has phosphoryl-group-transfer activity and/or phosphatase activity improved.

[Claim 2]The variant nucleoside 5'-phosphoric acid production enzyme according to claim 1 which is that to which the origin of an enzyme belongs to the Escherichia bacteria, the Morganella bacteria, Providencia bacteria, the Enterobacter bacteria, KUREBUJIERA group bacteria, or the Enterobacter bacteria.

[Claim 3]It carries out based on structure coordinates shown in atomic coordinate data produced by conducting X ray crystal structure analysis of the crystal of Escherichia BURATTAE origin acid phosphatase, The variant nucleoside 5'-phosphoric acid production enzyme according to claim 1 which presumed a bond form with nucleosides, such as inosine and guanosine, and a phosphoric acid compound of those and whose nucleoside 5'-phosphoric acid productivity improved by substitution, such as amino acid residue and/or a supplementary factor, an addition, and deletion.

[Claim 4]A following position of an amino acid sequence of Escherichia BURATTAE origin acid phosphatase (residue in Ser72 of Escherichia BURATTAE acid phosphatase, or Ser72 to 10A) : 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 115 and 140, 148-154, a variant nucleoside 5'-phosphoric acid production enzyme that change has produced in at least one position of 157, 179, and 183.

[Claim 5]With an enzyme which has phosphoryl-group-transfer activity and/or phosphatase activity, when amino acid sequence alignment with Escherichia BURATTAE origin acid phosphatase is carried out, A following position of an amino acid sequence of Escherichia BURATTAE origin acid phosphatase (residue in Ser72 of Escherichia BURATTAE acid phosphatase, or Ser72 to 10A) : 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 115 and 140, 148-154, a variant nucleoside 5'-phosphoric acid production enzyme that change has produced in at least one position corresponding to 157, 179, and 183.

[Claim 6]With an enzyme which has phosphoryl-group-transfer activity and/or phosphatase activity, when alignment with the three-dimensional structure of Escherichia BURATTAE origin acid phosphatase is performed by the TOREDDINGU method, A following position of an amino acid sequence of Escherichia BURATTAE origin acid phosphatase (residue in Ser72 of Escherichia BURATTAE acid phosphatase, or Ser72 to 10A) : 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 115 and 140, 148-154, a variant nucleoside 5'-phosphoric acid production enzyme that change has produced in at least one position corresponding to 157, 179, and 183.

[Claim 7]The origin of an enzyme is of the Enterobacter aerogenes origin, and in the amino acid sequence The 14th leucine residue, The 61st leucine residue, the 63rd alanine residue, the 64th glutamate residue, The 67th asparagine residue, the 69th serine residue, the 70th alanine residue, The 71st glycine residue, the 72nd glycine residue, the 101st isoleucine residue, The 102nd glutamate residue, the 133rd threonine residue, the 134th glutamate residue, A variant nucleoside 5'-phosphoric acid production enzyme in which at least one amino acid residue is replaced by other amino acid

residue among the 138th leucine residue, the 149th threonine residue, and the 151st isoleucine residue.

[Claim 8]. Became final and conclusive from an enzyme which has phosphoryl-group-transfer activity and/or phosphatase activity, or a spacial configuration produced by conducting X ray crystal structure analysis of the crystal of a complex of it and molybdcic acid. A manufacturing method of a variant nucleoside 5'-phosphoric acid production enzyme manufacturing an enzyme variant whose nucleoside 5'-phosphoric acid productivity improved an active site of this enzyme, and/or amino acid residue which is in less than 10A from it by carrying out substitution, an addition, and deletion.

[Claim 9]How to use structure coordinates of Escherichia BURATTAE origin acid phosphatase, and to manufacture inhibitor of phosphatase or phosphotransferase.

[Claim 10]One crystal of the complexes of an enzyme which has phosphoryl-group-transfer activity and/or phosphatase activity, or it and molybdcic acid.

[Claim 11]A crystal of Escherichia BURATTAE origin acid phosphatase which has space group  $P6_322$  of a hexagonal system.

[Claim 12]A crystal of Escherichia BURATTAE origin acid phosphatase G74 D/I153T enzyme variant which has space group  $P2_12_12_1$  of an ortho rhombic system.

[Claim 13]A crystal of a complex (reaction intermediate analog) of Escherichia BURATTAE origin acid phosphatase and molybdcic acid which have space group  $P3_121$  of a trigonal system.

[Claim 14]A gene which encodes an enzyme of a statement in any 1 paragraph of claims 1-7.

[Claim 15]A recombinant DNA containing the gene according to claim 14.

[Claim 16]A microorganism which holds the recombinant DNA according to claim 15.

[Claim 17]An enzyme given in any 1 paragraph of claims 1-7, or a microorganism containing it, Or a manufacturing method of nucleoside 5'-phosphoric acid making the microorganism according to claim 16 act on a nucleoside and a phosphate donor, making nucleoside 5'-phosphoric acid generate, and extracting this.

[Translation done.]

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## DETAILED DESCRIPTION

## [Detailed Description of the Invention]

[0001]

[Field of the Invention]This invention relates to a variant nucleoside 5'-phosphoric acid production enzyme whose nucleoside 5'-phosphoric acid productivity improved, and a manufacturing method for the same. This invention relates to enzymes useful to manufacture of the above-mentioned enzyme. This invention relates to the microorganism which holds the recombinant DNA containing the gene which encodes the useful aforementioned enzyme variant in the manufacturing method, and this gene, and this recombinant DNA, concerning the manufacturing method of nucleoside 5'-phosphoric acid. Nucleoside 5'-phosphoric acid is useful as a seasoning, medicines, and those raw materials. It is based on this invention having succeeded in the break through of the proteinic new spacial configuration by X ray crystal-structure-analysis art, and this spacial configuration has possibilities which are not restricted to a microorganism.

[0002]

[Description of the Prior Art]As a method of phosphorylating a nucleoside biochemically and manufacturing nucleoside 5'-phosphoric acid cheaply and efficiently, By making a specific microbial cell act on the phosphate donor chosen from the group which comprises a nucleoside and polyphosphoric acid (salt), phenylphosphoric acid (salt), and carbamyl phosphate under acid conditions, The method of generating nucleoside 5'-phosphoric acid efficiently is developed, without being accompanied by the byproduction of nucleoside 2'-phosphoric acid and a nucleoside 3'-phosphoric acid isomer (JP,7-231793,A). Then, the gene which encodes acid phosphatase is acquired from Escherichia BURATTAE (Escherichia blattae) and Morganella MORUGANI (Morganella morganii), It was checked by carrying out the extensive manifestation of this gene by Escherichia coli in gene engineering that the productivity of nucleoside 5'-phosphoric acid improves further. The structure of this acid phosphatase is shown in drawing 2. Drawing 2 Namely, Escherichia BURATTAE origin acid phosphatase. The amino acid sequence of (writing it as EB-AP hereafter) Morganella MORUGANI, Salmonella typhimurium (Salmonella typhimurium), They are an amino acid sequence of ZAIMO monas MOBIRISU (Zymomonas mobilis) origin acid phosphatase, and the aligned figure. The base sequence of the gene of each acid phosphatase and the amino acid sequence of the enzyme by which a code is carried out are shown in the array numbers 1-8 of an array table. An asterisk shows the saved residue by drawing 2. After aligning the field of secondary structure, it was shown with a stick. The portion enclosed with the line of the rectangular head shows the motif which is common between acid phosphatase families. The motif consists of three domains, the 1KXXXXXXRP array number 121, the 2PSGH array number 122, and 3SRXXXXHXXD array number 123\*\*. Here, X is arbitrary amino acid. This acid phosphatase (drawing 2) has the superior phosphatase activity which decomposes nucleoside 5'-phosphoric acid into a nucleoside in a wild type although it has phosphoryl-group-transfer activity, and there was a fault into which the accumulated nucleoside 5'-phosphoric acid will be decomposed. Then, generate many enzyme variants at random and the variant acid phosphatase whose phosphoryl-group-transfer activity improved relatively as compared with phosphatase activity from the inside is found out, It was shown by by carrying out the extensive manifestation of this variant acid phosphatase gene that the productivity of nucleoside 5'-phosphoric acid improves by leaps and bounds (JP,9-37785,A). The compatibility of this variant phosphatase over a nucleoside is



improving.

It is thought that phosphoryl-group-transfer activity has been improved by that cause.

The above-mentioned Escherichia BURATTAE origin variant acid phosphatase (= G74 D/I153T enzyme variant), Although phosphoryl-group-transfer activity is weaker than G72 D/I151T enzyme variant in which Morganella MORUGANI origin acid phosphatase (MM-AP) corresponds, The 10 residue substitution L63 Q/A65 Q/E66 A/N69 D/S71 A/S72 A/G74 D/T135 K/E136 D/I153T enzyme variant which replaced eight amino acid residue by the amino acid of MM-AP corresponding on the primary structure (henceforth) It was only shown that 10 residue substitution variant EB-AP and description acquire phosphoryl-group-transfer activity almost equivalent to G72 D/I151T variant MM-AP (JP,10-201481,A).

[0003]

[Problem(s) to be Solved by the Invention]The G74 D/I153T variant enzyme gene of the Escherichia BURATTAE origin acid phosphatase (EB-AP) whose above-mentioned productivity improved, the method of producing nucleoside 5'-phosphoric acid is established by carrying out the extensive manifestation of the 10 residue substitution variant enzyme gene by Escherichia coli -- having had (JP,9-37785,A, JP,10-201481,A) -- variant EB-AP whose productivity improved is desired. This invention makes it a technical problem to aim at further improvement in nucleoside 5'-phosphoric acid productivity by designing variant EB-AP based on the three-dimensional structure of EB-AP.

[0004]

[Means for Solving the Problem]If this invention is outlined, it will be as enumerating below.

In a nucleoside 5'-phosphoric acid production enzyme, (1) One Lys residue, Two Arg residue and two His residue exist, and there is distance between such Calpha within limits shown in *drawing 1*, And a variant nucleoside 5'-phosphoric acid production enzyme whose nucleoside 5'-phosphoric acid productivity of an enzyme which has a space which a nucleoside combines near the, and which has phosphoryl-group-transfer activity and/or phosphatase activity improved.

(2) A variant nucleoside 5'-phosphoric acid production enzyme given in (1) paragraph which is that to which the origin of an enzyme belongs to the Escherichia bacteria, the Morganella bacteria, Providencia bacteria, the Enterobacter bacteria, KUREBUJIERA group bacteria, or the Enterobacter bacteria.

(3) It carries out based on structure coordinates shown in atomic coordinate data produced by conducting X ray crystal structure analysis of the crystal of EB-AP, A variant nucleoside 5'-phosphoric acid production enzyme given in (1) paragraph given nucleoside 5'-phosphoric acid productivity improved by presuming a bond form with nucleosides, such as inosine and guanosine, and carrying out substitution, such as amino acid residue and/or a supplementary factor, an addition, and deletion.

(4) . A following position of an amino acid sequence of EB-AP. amino acid Ser72 of EB-AP. Or residue in Ser72 to 10A : 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 115 and 140, 148-154, a variant nucleoside 5'-phosphoric acid production enzyme that change has produced in at least one position of 157, 179, and 183.

(5) With an enzyme which has phosphoryl-group-transfer activity and/or phosphatase activity. When amino acid sequence alignment with EB-AP is carried out, A following position of amino acid sequence \*\* of EB-AP. amino acid Ser72 of EB-AP. Or residue in Ser72 to 10A : 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 115 and 140, 148-154, a variant nucleoside 5'-phosphoric acid production enzyme that change has produced in at least one position of 157, 179, and 183.

(6) With an enzyme which has phosphoryl-group-transfer activity and/or phosphatase activity. When alignment with the three-dimensional structure of EB-AP is performed by the TOREDDINGU method, A following position of amino acid sequence \*\* of EB-AP. amino acid Ser72 of EB-AP. Or residue in Ser72 to 10A : 16, 67-76, 78-79, 96, 99-100, 102-104, 106-108, 115 and 140, 148-154, a variant nucleoside 5'-phosphoric acid production enzyme that change has produced in at least one position of 157, 179, and 183.

[0005](7) The origin of an enzyme is of the Enterobacter aerogenes origin, In the amino acid sequence, the 14th leucine residue, the 61st leucine residue, The 63rd alanine residue, the 64th glutamate residue, the 67th asparagine residue, The 69th serine residue, the 70th alanine residue, the 71st glycine residue, The 72nd glycine residue, the 101st isoleucine residue, the 102nd glutamate

residue, The 133rd threonine residue, the 134th glutamate residue, the 138th leucine residue, A variant nucleoside 5'-phosphoric acid production enzyme in which at least one amino acid residue is replaced by other amino acid residue among the 149th threonine residue and the 151st isoleucine residue.

(8) An enzyme which has phosphoryl-group-transfer activity and/or phosphatase activity, . Or became final and conclusive from a spacial configuration produced by conducting X ray crystal structure analysis of the crystal of a complex of it and molybdc acid. amino acid residue (constituted by Lys1 \*\* and two Arg(s) His two) located in an active site of this enzyme -- and/or -- and amino acid residue in less than 10A by carrying out substitution, an addition, and deletion, A manufacturing method of a variant nucleoside 5'-phosphoric acid production enzyme manufacturing an enzyme variant whose nucleoside 5'-phosphoric acid productivity improved.

(9) How to use structure coordinates of Escherichia BURATTAE origin acid phosphatase, and to manufacture inhibitor of phosphatase or phosphotransferase.

[0006](10) One crystal of the complexes of an enzyme which has phosphoryl-group-transfer activity and/or phosphatase activity, or it and molybdc acid.

(11) A crystal of EB-AP which has space group  $P6_322$  of a hexagonal system.

(12) A crystal of EB-AP G74 D/I153T enzyme variant which has space group  $P2_12_12_1$  of an ortho rhombic system.

(13) A crystal of a complex (reaction intermediate analog) of EB-AP and molybdc acid which have space group  $P3_121$  of a trigonal system.

[0007](14) A gene which encodes an enzyme of a statement in any 1 paragraph of (1) - (7) paragraph.

(15) A recombinant DNA which contains a gene of a statement in (14) paragraphs.

(16) A microorganism which holds a recombinant DNA of a statement in (15) paragraphs.

[0008](17) An enzyme given in any 1 paragraph of (1) - (7) paragraph, or a microorganism containing it, Or a manufacturing method of nucleoside 5'-phosphoric acid making a microorganism given in (16) paragraphs act on a nucleoside and a phosphate donor, making nucleoside 5'-phosphoric acid generate, and extracting this.

[0009]Based on the three-dimensional structure of EB-AP, this invention builds a bond form model with a nucleoside, and provides a production method of nucleoside 5'-phosphoric acid using variant EB-AP designed based on it.

[0010]

[Embodiment of the Invention]Hereafter, this invention is explained concretely.

(1) In order to determine the proteinic three-dimensional structure by X ray crystal structure analysis, it is necessary to crystallize protein (details were shown in Example 1-3). In order to crystallize protein, pH, the kind of buffer, the concentration of a buffer and the kind of precipitant, the concentration of a precipitant, the concentration of additive agents, such as metal, the concentration of protein, proteinic purity, etc. must determine many parameters by trial and error. Therefore, before obtaining a crystal, usually the time for several months - several years will be taken, and there is also a case where a crystal is not obtained against a great labor, plentifully. although crystallization is indispensable for three-dimensional structure determination -- other than this -- being also alike -- there are a purification method of a proteinic high grade, stable Conservation Act whose protease resistance it is high-density and is strong, and also usefulness industrial as a process before fixed use of an enzyme.

(2) Irradiate the produced crystal with X-rays and collect diffraction data. A crystal protein has plentifully a case where X-ray irradiation receives a damage and diffraction ability deteriorates. In that case, a crystal is rapidly cooled at about -173 \*\*, and the low temperature thermometry which collects diffraction data in the state has been spreading recently. in addition -- a crystal does not collapse when cooling -- a system -- it is necessary to devise solvent composition so that the whole may become vitrified

(3) In addition to diffraction data, topology is needed in order to conduct crystal structure analysis. Since the spacial configuration of EB-AP of the protein of a relative is strange, a phase problem must be solved by a heavy atom isomorphous replacement method. A heavy atom isomorphous

replacement method is a method of introducing a metal atom with big atomic numbers, such as mercury and platinum, into a crystal, and acquiring topology using contribution of X diffraction DETAHE of the big X-ray scattering ability of a metal atom. If the spacial configuration of wild type EB-AP is determined, the crystal structure of analogs, such as an enzyme variant and a reaction intermediate analog, can be determined with the molecular replacement method which used it. A molecular replacement method is the technique of performing structure determination in the protein which wants to determine a crystal structure using the spacial configuration, when the spacial configuration of the protein of a relative is known. For example, if the spacial configuration of the wild type of a certain protein is known, a molecular replacement method is applicable to the crystal structure determination of the variant protein or the protein by which chemical modification was carried out. About G74 D/I153T variant EB-AP, a crystal structure is determined for a molecular mechanism break through of the improvement in nucleoside compatibility by two amino acid substitution. About a reaction intermediate analog, in order to build a bond form model with a nucleoside, a crystal structure is determined. A nucleoside is changed into nucleoside 5'-phosphoric acid after the phosphate group supplied combines with EB-AP in the state where the covalent bond was carried out, i.e., reaction intermediate. Since the reaction intermediate of EB-AP was unstable, the structure could not be caught, but since it was not hydrolyzed instead of phosphoric acid when molybdic acid was the reaction intermediate analog which carried out the covalent bond, I thought that structure determination was possible. Details were shown in Examples 4, 6, and 7.

[0011](4) On computer graphics (CG), based on the molybdic acid connecting position in the three-dimensional structure of a reaction intermediate analog, make a nucleoside fit the hollow of the neighborhood and build a bond form model (drawing 3). A program like QUANTA of MSI (United States) and INSIGHT II is used for construction of a model, for example. Drawing 3 is a photograph which shows the crystal structure of the above-mentioned bond form model. Details were shown in Examples 5 and 8.

(5) Observe coupled models well and design the variation which increases compatibility with a nucleoside. In order to raise compatibility, a means to enhance a canal interaction, an electrostatic interaction, a hydrogen bond, a pi-pi interaction (interaction of the magnetic fields which the ring current of an aromatic ring generates), and a CH/pi interaction (interaction of the magnetic field which the ring current of an aromatic ring and the electron of a methyl group generate) can be considered. Since it is predicted that Ser72 interacts with the base of a nucleoside most strongly, It seems that the substitution to Phe, Tyr, and Trp enhances a hydrophobic interaction and a pi/pi interaction, the substitution to Val, Ile, and Leu enhances a hydrophobic interaction and a CH/pi interaction, and the substitution to Glu and Asp reinforces an electrostatic interaction and a hydrogen bond. A hydrophobic interaction etc. may be enhanced by the substitution to other amino acid, especially the substitution to the amino acid which has a more nearly long-chain side chain. It is expected that a pi/pi interaction will be formed between the aromatic ring of amino acid residue and the base of a nucleoside which were replaced also by replacing Leu16, Ser71, Ser73, and Glu104 by Phe, Tyr, and Trp. Formation of a hydrogen bond with the ribose of a nucleoside is expected by replacing Ile103 and Thr153 by more nearly long-chain hydrophilic residue. Since an opening will produce inside protein if it replaces by amino acid residue with small side chains [151 / which was located near the nucleoside binding site and has been buried in the inside of protein / Thr], such as Ser, Ala, and Gly, The pliability of a nucleoside binding site is expected whether to be able to take increase and the conformation which was suitable by combination with a nucleoside. Although Leu140 has separated not less than 10A from Ser72, it is located in the nearest to a phosphate bond part in the spacial configuration of a reaction intermediate analog. Therefore, when replacing this residue, the structure around a phosphate bond part in reaction intermediate changed, and it was thought by extension that influence also attained to the structure of a nucleoside binding site and fluctuation. If it replaces without Lys which has bulkier Phe and positive charge for this residue, and Glu which has a negative charge, it is hoped that compatibility with a nucleoside may change. The above-mentioned variation is introduced to G74 D/I153T variant EB-AP at the beginning. However, the enzyme variant made into the object of introduction is not restricted to G74 D/I153T variant EB-AP. For example, it is also possible to introduce variation into 10 residue substitution variant EB-AP. Variation is carried out to introducing to G74 D/I153T variant EB-AP. In this case, the enzyme variant produced turns

into 3 residue substitution enzyme variant. Details were shown in Example 9.

(6) Produce the plasmid which contains the gene which encodes variant EB-AP by the PCR method. A plasmid is introduced into *Escherichia coli* (*Escherichia coli*) JM109, and variant EB-AP is made to produce. Km value which becomes an index of compatibility to the inosine of variant EB-AP, and the phosphoryl-group-transfer activity which changes inosine into 5'-inosinic acid are measured, and the performance of variant EB-AP is evaluated. It is thought that it depends for the quantity of production of nucleoside 5'-phosphoric acid on Km value much. Pyrophoric acid reacts to EB-AP, phosphoric acid ion breaks away, and if a water molecule attacks this after the reaction intermediate of the form in which the phosphate group carried out the covalent bond to EB-AP is formed, a phosphate group will separate (phosphatase reaction). It means that pyrophoric acid was consumed vainly, without generating nucleoside 5'-phosphoric acid. On the other hand, if a nucleoside attacks reaction intermediate, a phosphate group will form a nucleoside and phospho monoester binding, and the generated nucleoside 5'-phosphoric acid will secede from EB-AP (phosphoryl-transfer reaction). It means that pyrophoric acid was utilized for nucleoside 5'-phosphoric acid generation. That is, if water and a nucleoside scramble for reaction intermediate, water wins and a nucleoside will win in phosphatase activity, phosphoryl-group-transfer activity will be demonstrated. If the compatibility over EB-AP of a nucleoside goes up (i.e., if Km value falls), a possibility that a phosphoryl-transfer reaction will be performed will become high. If the hydrophobicity near a phosphate bond part is improved and water becomes difficult to approach, phosphatase activity will become weaker and phosphoryl-group-transfer activity will become strong relatively. Details were shown in Example 10.

(7) Conduct the experiment which produces 5'-inosinic acid from inosine using *Escherichia coli* JM109 which introduced the plasmid containing the variant EB-AP gene in which Km value fell to and phosphoryl-group-transfer activity went up. A reaction is performed at 30 °C for 45 hours, and aging of 5'-inosinic acid quantity of production is monitored. Details were shown in Example 12.

(8) If the variation part in which Km is reduced is found out, by combining two or more residue, the compatibility over a nucleoside can improve further and the enzyme variant which became high [ productivity ] can be produced. Two or more mutation sites can be introduced by repeating site-specific mutation cumulatively. If the primer from which the portion of the base which encodes the amino acid residue which introduces variation in the case of introduction of site-specific mutation became a mix base is used, the library of a variant gene where specific amino acid residue was replaced by all the amino acid can be created. If the primer of a mix base is used for two or more parts and variation is introduced, the library of the variant gene which encodes the enzyme variant of various sorts dramatically can be created. Thus, the method of selecting the variant which introduced the library of the built gene into *Escherichia coli* and with which the amino acid substitution of high activity was combined from the library made to reveal is also effective.

[0012] If it is an enzyme with the space which the same active site and nucleoside as EB-AP can combine also except EB-AP, there is potential which can be used for production of nucleoside 5'-phosphoric acid. An active site has indispensable amino acid residue with activity, and must be arranged by the space position relation with suitable them. In EB-AP, Lys115, Arg122, His150, Arg183, and His189 are indispensable with activity, and it is possible to specify space position relations with the distance between C $\alpha$  of these 5 residue. In this invention, since three EB-AP crystal structures, a wild type, G74 D/I153T variant, and a reaction intermediate analog, were determined, C $\alpha$  interatomic distance of the activity residue in each structure was measured, and Table 1 was created. Since each distance distribution of Table 1 had the width which is about 1Å, when beyond a distance (Table 1, a minimum) shorter 1Å than the shortest distance was below a distance (Table 1, a maximum) longer 1Å than longest distance, I thought that the active site called for could be formed. The physical relationship of five residue was shown in drawing 1 with the distance between C $\alpha$  of the maximum and the minimum. In MM-AP which is a relative enzyme of EB-AP, it was shown in Example 15 that it was checked that all the interatomic distances between activity residue have fitted in the range specified from the spacial configuration of EB-AP. By this example, although the example of G72 D/I151T variant instead of a wild type was shown, it is thought that there is no big difference to the spacial configuration of an active site at the same wild type and variant of an enzyme. This guess is supported by that the structure of the active site of the wild type of EB-AP and G74 D/I153T variant is fundamentally the same (refer to Table 1). In order to

phosphorylate a nucleoside and to change into nucleoside 5'-phosphoric acid, just the active site that comprises the 5 above-mentioned residue is insufficient, and a nucleoside must be able to combine with a suitable position in it. In EB-AP, a grooved space suitable for a nucleoside joining near the binding site of a phosphate group together exists in the molecule surface. [(drawing 3): It can display on computer graphics (CG) using drawing 10 in which the atomic coordinates of which attachment was done are shown - drawing 45. ]This slot is specified as a space surrounded by 4 residue of Leu16, Ser72, Glu104, and His189. Even if it has an active site, the enzyme without the suitable space which a nucleoside combines is unsuitable as a nucleoside 5'-phosphoric acid production enzyme.

[0013]

[Table 1]

		野生型	G74D/1153T 変異型	反応中間体 アナログ	下限	上限
Lys115	Arg122	11.6Å	11.6Å	11.4Å	10.4Å	12.6Å
	His150	12.4Å	12.3Å	12.8Å	11.3Å	13.8Å
	Arg183	16.4Å	16.3Å	15.5Å	14.5Å	17.4Å
	His189	12.6Å	12.1Å	11.7Å	10.7Å	13.6Å
Arg122	His150	13.2Å	13.6Å	14.2Å	12.2Å	15.2Å
	Arg183	10.4Å	10.5Å	10.8Å	9.4Å	11.8Å
	His189	5.6Å	5.5Å	5.7Å	4.5Å	6.7Å
His150	Arg183	8.4Å	8.8Å	7.7Å	6.7Å	9.8Å
	His189	9.8Å	10.0Å	10.0Å	8.8Å	11.0Å
Arg183	His189	5.5Å	6.8Å	5.7Å	4.5Å	6.8Å

[0014]This invention provides preferably the substitution to other amino acid of Ser72, and Phe, Tyr, Trp, Val, Leu, Glu, Asp, Gln, Met, Thr, Arg and variant EB-AP that performed substitution to any one amino acid of Lys. The residue (residue number: 16, 70-71, 73-76 and 100, 102-104, 106-108, 115, 148-154, 183) in Ser72 to 10A has a dramatically high possibility of interacting with a nucleoside, Variant EB-AP which performed substitution to other amino acid of these amino acid residue is provided. It includes here not only when amino acid being artificially replaced by substitution, but selecting other acid phosphatase belonging to the same enzymatic family as EB-AP which substitution produced in the nature. However, variant EB-AP containing mutational sites other than the above-mentioned amino acid residue can also provide this invention.

[0015]Also in other acid phosphatase belonging to the same enzymatic family as EB-AP, if amino acid variation of homologous is given, it is possible to use for manufacture of nucleoside 5'-phosphoric acid. However, the amino acid residue of EB-AP is not necessarily equivalent to the amino acid residue of the same number in other acid phosphatase. For example, Ser72 of EB-AP corresponds to Ala70 in MM-AP. Matching of the amino acid residue of two different protein, If the homology of both amino acid sequence is not less than about 20% and it is alignment (Sequence Alignment) of amino acid sequences, and about 20% or less, it will become clear by alignment (Threading) of the three-dimensional structure and an amino acid sequence. The former can perform the latter, such as BLAST, by programs, such as INSIGHT II. Amino acid sequence alignment of EB-AP and Enterobacter aerogenes (Enterobacter aerogenes) origin acidity HOFATAZE (EA-AP) using BLAST was shown in Example 14. BLAST should just obtain the file in accordance with the computer used among the files which exist in /blast/executable from ncbi.nlm.nih.gov using FTP. Details are described by <http://genome.nhgri.nih.gov/blastall/blast#install> about operation information.

[0016]Although attained by the improvement in compatibility with a nucleoside in many cases, it is attained by the shift of optimal pH, thermal stability improvement, etc. besides it, and deals in the improvement in nucleoside 5'-phosphoric acid productivity. The shift of optimal pH can be attained by changing pK of activity residue. [Protein engineering (Protein Engng.), the 1st volume, the 383-388th page (1998)]. Substitution to the glycine residue of the residue in which thermal stability improvement takes introduction of proline residue, and a counterclockwise twining helical structure [Protein

engineering, the 6th volume, the 85-91st page (1993)] The opening inside protein is filled. [Biochemistry (Biochemistry), the 32nd volume, the 6171-6178th page (1993)] \*\*\*\*\* achievement is possible. It is effective in order to produce the variant whose nucleoside 5'-phosphoric acid productivity the compatibility of this spacial configuration of the nucleoside improved and improved, as explained to details above, but. This spacial configuration is effective not only in the compatibility over the nucleoside of an enzyme but changing compatibility with a phosphate donor. This enzyme can use various phosphoric ester compounds, such as polyphosphoric acid (salt), phenylphosphoric acid (salt), acetyl phosphate (salt), and carbamyl phosphate (salt), as a phosphate donor as indicated to JP,9-37785,A, but. It is possible to extend the substrate specificity of a phosphate donor or to raise the capacity factor of phosphoric acid by designing the variation which increases compatibility with a phosphoric ester compound in a way similar with having designed the variation which increases compatibility with a nucleoside.

[0017]

[Example] Hereafter, although an example explains this invention still more concretely, this invention is not limited to these examples.

[0018] Example 1 It crystallized using steamy diffusion with the crystallization hanging drop method of wild type EB-AP. 20mM buffer solution (pH 8.0) of sodium phosphate containing wild type EB-AP (concentration of 10mg/ml), the 100mM buffer solution of the trischloride containing the polyethylene glycol 400 of 45 (w/v %) -- an equivalent amount -- every (each 7-10microl). the well which filled 100mM buffer solution 500mul of the trischloride which carries out dropping mixing on the cover glass [SHIRIKONAIZEISHON / cover glass], and contains the polyethylene glycol 400 of 45 (w/v %) -- it covered so that a mixed liquor drop might fish and fall on (well), and it settled at 20 \*\*. The crystal deposited 2 or 3 days afterward, and, two weeks afterward, it grew up to be a crystal of the shape of a hexagonal prism of a measurable size (about 0.3x0.3x1.2 mm) from one week. On the occasion of X-ray-data measurement, the crystal was moved to the 100mM buffer solution (pH 8.0) of the trischloride containing the polyethylene glycol 400 of 50 (w/v %). This crystal needed to care about the following point on handling. 1) Since a crystal collapsed very easily by contacting a container and tools from a drop (droplet) when taking out a crystal, the crystallization gestalt of the sitting dropping method could not be used (a crystal grows), but used the hanging drop method described here. 2) At ordinary temperature measurement, since a crystal deteriorated during measurement and resolution fell gradually, it needed to be measured under the low temperature service. Time until it mounts a crystal on a stage was shortened as much as possible, and it devised so that it might not expose to air. Using X-ray diffractometer R-Axis IIC of Rigaku, X diffraction data was collected and the crystallographic parameter was determined. The space group was set to P6<sub>3</sub>22 and the grating constant became a=b=124.4Å and c= 97.7 Å. If it assumes that one subunit of the molecular weight 25000 is included in an unsymmetrical unit, the moisture content of a crystal will be 72%.

[0019] It crystallized using steamy diffusion with the crystallization hanging drop method of example 2 G74 D/I153T variant EB-AP. 20mM buffer solution (pH 8.0) of the trischloride containing G74 D/I153T enzyme variant (concentration of 20mg/ml), 20mM buffer solution of the trischloride containing the polyethylene glycol 400 of 38 (w/v %) -- an equivalent amount -- every (each 5microl). Dropping mixing was carried out on the cover glass [SHIRIKONAIZEISHON / cover glass], it covered so that a mixed liquor drop might fish and fall on the well which filled 20mM buffer solution 500mul of the trischloride containing the polyethylene glycol 400 of 38 (w/v %), and it settled at 20 \*\*. The crystal deposited 2 or 3 days afterward, and, one week afterward, it grew up to be a plate crystal of a measurable size (about 0.7x0.4x0.2 mm). On the occasion of X-ray-data measurement, the crystal was moved to the 100mM buffer solution (pH 8.0) of the trischloride containing the polyethylene glycol 400 of 50 (w/v %). Using X-ray diffractometer R-Axis IIC of Rigaku, X diffraction data was collected and the crystallographic parameter was determined. The space group became P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, and the grating constant became a= 138.0 Å, b= 168.3 Å, and c= 58.2 Å. If it assumes that one hexamer molecule of the molecular weight 150000 is included in an unsymmetrical unit, the moisture content of a crystal will be 64%.

[0020] Example 3 It crystallized using the cocrystal-ized method for having used steamy diffusion by the crystallization sitting dropping method of the complex (reaction intermediate analog) of wild type

EB-AP and molybdic acid. 20mM buffer solution (pH 8.0) of sodium phosphate containing wild type EB-AP (concentration of 10mg/ml), the 100mM buffer solution of the trischloride containing the polyethylene glycol 400 of 40 (w/v %), and sodium molybdate of 1mM -- an equivalent amount -- every (each 15microl). Dropping mixing was carried out and it settled on the hollow of the bridge installed in the well which filled 500micro of 100mM buffer solution (pH 8.0) of the trischloride containing the polyethylene glycol 400 of 40 (w/v %) at 20 \*. The crystal deposited two to three days afterward, and, two weeks afterward, it grew up to be a crystal of the shape of a diamond-shaped rice cake of a measurable size (about 0.3x0.3x0.3 mm) from one week. On the occasion of X-ray-data measurement, the crystal was moved to the 100mM buffer solution (pH 8.0) of the trischloride containing the polyethylene glycol 400 of 50 (w/v %). Using X-ray diffractometer R-AXIS IIc of Rigaku, X diffraction data was collected and the crystallographic parameter was determined. The space group was set to  $P3_121$  and the grating constant became  $a=b=86.6\text{\AA}$  and  $c=205.3\text{\AA}$ . If it assumes that three subunits of the molecular weight 25000 are included in an unsymmetrical unit, the moisture content of a crystal will be 58%.

[0021]Example 4 The X diffraction data to a maximum of 1.9Å of crystal-structure-analysis resolution data of wild type EB-AP was measured. In ordinary temperature, since the damage by the exposure of X-rays was intense, the crystal measured by cooling quickly at -173 \*. The Shigehara child derivative was screened by dipping a crystal into the solution of heavy metal salt. The diffraction data of the Shigehara child derivative crystal was obtained using Rigaku R-AXIS IIc.  $K_2PtCl_4$  found out giving the good Shigehara child same type crystal from the difference Fourier figure with native data. By using the program RSPS, the coordinates of the only platina binding site of  $K_2PtCl_4$  were searched for. It asked for the phase which carries out elaboration of these coordinates by the program MLPHARE, and is calculated. It asked for five mercury binding sites of the 2nd Shigehara child derivative  $KHgI_4$ -KI using this phase. After carrying out elaboration of the Shigehara child parameter of both  $K_2PtCl_4$  and  $KHgI_4$ -KI simultaneously using MLPHARE, using program DM, solvent smoothing and histogram matching were performed and the phase was improved. Incidentally, anomalous dispersion data was also used about  $K_2PtCl_4$ . The electron density map calculated using this good phase was dramatically clear, and was able to fit almost all amino acid residue finely. The first model was built using the program QUANTA on the electron density map created with 2.8Å resolution, and performed structure refinement using program X-PLOR. Electron density was not observed and 6 residue in the end of N, the 135 to 136th residue, and 1 residue in the end of C were not able to determine structure uniquely. The final model (drawing 4 - drawing 6) by which elaboration was carried out with 1.9Å resolution contains all the 222 in 231 residue residue, 236 water molecules, and one molecule of sulfate ion. Sulfate ion originates in the ammonium sulfate used in refining processes. It is considered a match by the phosphate bond part of an active center.

The crystallographic reliability factor (R factor) using reflection of 8-1.9Å resolution became 21.5%. The average temperature factor became  $26\text{\AA}^2$  about the protein atom, and became  $45\text{\AA}^2$  about the water molecule. When Ramachandran plot was created using the program PROCHECK, it was shown in the field where 93% of residue other than a glycine is the most preferred that 7% is located in a field desirable next. One subunit is contained in an unsymmetrical unit and a hexamer is formed of crystallographic symmetry. Atomic coordinates were shown in drawing 10 - drawing 45.

[0022]Drawing 4 is a CG photograph which shows the crystal structure of the hexamer molecule of EB-AP. The flow of alpha carbon atom was displayed with the ribbon model. The sulfate ion which marks an active center was displayed with the ball model. Drawing 5 is a CG photograph which shows the crystal structure of the subunit of EB-AP. The flow of alpha carbon atom was displayed with the ribbon model. The sulfate ion which marks an active center was displayed with the ball model. Drawing 6 is a figure showing the active site architecture of EB-AP. Sulfate ion was shown in the center. The dotted line showed the hydrogen bond. Drawing 10 is a figure showing the crystallography data (1) of the structure of EB-AP. Drawing 11 is a figure showing the crystallography data (2) of the structure of EB-AP. Drawing 12 is a figure showing the crystallography data (3) of the structure of EB-AP. Drawing 13 is a figure showing the crystallography data (4) of the structure of EB-AP. Drawing 14 is a



figure showing the crystallography data (5) of the structure of EB-AP. Drawing 15 is a figure showing the crystallography data (6) of the structure of EB-AP. Drawing 16 is a figure showing the crystallography data (7) of the structure of EB-AP. Drawing 17 is a figure showing the crystallography data (8) of the structure of EB-AP. Drawing 18 is a figure showing the crystallography data (9) of the structure of EB-AP. Drawing 19 is a figure showing the crystallography data (10) of the structure of EB-AP. Drawing 20 is a figure showing the crystallography data (11) of the structure of EB-AP. Drawing 21 is a figure showing the crystallography data (12) of the structure of EB-AP. Drawing 22 is a figure showing the crystallography data (13) of the structure of EB-AP. Drawing 23 is a figure showing the crystallography data (14) of the structure of EB-AP. Drawing 24 is a figure showing the crystallography data (15) of the structure of EB-AP. Drawing 25 is a figure showing the crystallography data (16) of the structure of EB-AP. Drawing 26 is a figure showing the crystallography data (17) of the structure of EB-AP. Drawing 27 is a figure showing the crystallography data (18) of the structure of EB-AP. Drawing 28 is a figure showing the crystallography data (19) of the structure of EB-AP. Drawing 29 is a figure showing the crystallography data (20) of the structure of EB-AP. Drawing 30 is a figure showing the crystallography data (21) of the structure of EB-AP. Drawing 31 is a figure showing the crystallography data (22) of the structure of EB-AP. Drawing 32 is a figure showing the crystallography data (23) of the structure of EB-AP. Drawing 33 is a figure showing the crystallography data (24) of the structure of EB-AP. Drawing 34 is a figure showing the crystallography data (25) of the structure of EB-AP. Drawing 35 is a figure showing the crystallography data (26) of the structure of EB-AP. Drawing 36 is a figure showing the crystallography data (27) of the structure of EB-AP. Drawing 37 is a figure showing the crystallography data (28) of the structure of EB-AP. Drawing 38 is a figure showing the crystallography data (29) of the structure of EB-AP. Drawing 39 is a figure showing the crystallography data (30) of the structure of EB-AP. Drawing 40 is a figure showing the crystallography data (31) of the structure of EB-AP. Drawing 41 is a figure showing the crystallography data (32) of the structure of EB-AP. Drawing 42 is a figure showing the crystallography data (33) of the structure of EB-AP. Drawing 43 is a figure showing the crystallography data (34) of the structure of EB-AP. Drawing 44 is a figure showing the crystallography data (35) of the structure of EB-AP. Drawing 45 is a figure showing the crystallography data (36) of the structure of EB-AP.

[0023] Example 5 Since it exceeds 100mM, Km value of compatibility to wild type EB-AP and EB-AP of the guess inosine of the bond form model of 5'-inosinic acid is not so high as it can determine a bond form by X ray crystal structure analysis. After actually soaking the compound used as inhibitor of EB-AP, such as glucose 6-sulfate and adenosine thio monophosphate, into the crystal of wild type EB-AP, collected X diffraction data, and created the electron density map, but. The electron density corresponding to these compounds was not observed. Then, we decided to guess the bond form of 5'-inosinic acid and EB-AP (what is called a docking study) using computer graphics. The program used QUANTA. Among the crystal structure, since sulfate ion was found out in the center of an active site, the phosphate group of 5'-inosinic acid was piled up here. Since it was known that G74D and the variation of I153T will reduce Km value to EB-AP of 5'-inosinic acid, it judged that 5'-inosinic acid was combined with the place in which a long distance is not from G74 and I153, and the position of 5'-inosinic acid was decided. The atom which constitutes 5'-inosinic acid, and the atom which constitutes EB-AP were kept from colliding mutually in that case. In this way, in the built model, if I153 is set to T, the gamma acid matter atom of the side chain of threonine and 2' hydroxyl group of the ribose of inosine which were replaced will form a hydrogen bond. When an electrostatic potential indication of EB-AP is given using the program GRASP, the inosine base which is tinged with positive charge is interacting with the field which is tinged with the negative charge on the EB-AP molecule surface.

It was suggested that a model will seemingly be reasonable.

[0024] The ratio of phosphoryl-group-transfer activity [ as opposed to phosphatase activity in crystal-structure-analysis G74 D/I153T variant EB-AP of example 6 G74 D/I153T variant EB-AP ] is increasing.



In connection with it, the production capacity of nucleoside 5'-phosphoric acid is also improving. It is considered as a cause that it improved that this Km value with a nucleoside fell, i.e., compatibility with a nucleoside. When determining the crystal structure of this variant EB-AP and comparing with the crystal structure of wild type EB-AP, it was expected that the molecular mechanism of the improvement in compatibility with a nucleoside would be clarified. At ordinary temperature, the X diffraction data to a maximum of 2.4Å resolution data was measured. It was expected that estimate from the molecular weight of the volume of a unit cell, a space group, and an enzyme, and one molecule of a hexamer is contained in an unsymmetrical unit. Then, it analyzed with the molecular replacement method using the program amore by making hexamer structure of wild type EB-AP into a search model. In rotation search, the data of 10-4Å resolution was used for the data of 10-3Å resolution in translation search. The correct answer of both searches appeared as top peaks. When elaboration was performed by using a molecule as a rigid body, the R factor fell to 37.3%. Then, it carried out by having repeated the structure correction on the graphics using QUANTA, and the structure refinement using X-PLOR, and the model of 19.9% of the R factor was obtained in 10-2.4Å resolution. When the coupled models of 5'-inosinic acid and G74 D/I153T variant EB-AP were created by the same method as Example 5, it was expected that the gamma acid matter atom of the side chain of replaced Thr153 forms the hydroxyl group and hydrogen bond of a ribose of inosine. By comparing a temperature factor showed that the direction of G74 D/I153T variant EB-AP was large compared with a wild type in fluctuation of the loop containing Asp74 to which one more substitution was performed. Although it is expected that this loop interacts with the base of inosine, when fluctuation became large, a possibility of becoming easy to carry out combination with a base is suggested.

[0025]Example 7 In the enzyme reaction of crystal-structure-analysis EB-AP of the complex (reaction intermediate analog) of wild type EB-AP and molybdic acid, first, monoester phosphate combination is cut and a phosphate group forms His189 of activity residue, and a covalent bond. The enzyme molecule of this state is called reaction intermediate. Promptly, reaction intermediate receives the attack by water or alcohol, and, as a result, phosphoric acid ion secedes from it. If water attacks, phosphatase activity will be demonstrated, and if alcohol attacks, phosphoryl-group-transfer activity will be demonstrated. Anyway, reaction intermediate is unstable and it is impossible to determine the structure by X ray crystal structure analysis. However, since that (reaction intermediate analog), as for, molybdic acid carried out the covalent bond to His189 instead of phosphoric acid does not receive the attack by water, it exists in stability. In a phosphoryl-transfer reaction, a phosphate acceptor combines with reaction intermediate and monoester phosphate combination is formed. Therefore, it is more suitable to use reaction intermediate structure rather than isolation mold structure in the purpose of presuming a bond form with a nucleoside. Crystal structure analysis of the reaction intermediate analog was conducted in order to perform a docking study with reaction intermediate and a nucleoside. At ordinary temperature, the X diffraction data to a maximum of 2.4Å resolution data was measured. It was expected that estimate from the molecular weight of the volume of a unit cell, a space group, and an enzyme, and three half of a hexamer, i.e., subunits, is included in an unsymmetrical unit. Then, with the threefold rotation axis, the trimer structure where each other was connected was created and it was considered as the search model of the molecular replacement method. In rotation search, the data of 10-4Å resolution was used for the data of 10-3Å resolution in translation search. The correct answer of both searches appeared as top peaks. When elaboration was performed by using a molecule as a rigid body, the R factor fell to 42.4%. Then, it carried out by having repeated the structure correction on the graphics using QUANTA, and the structure refinement using X-PLOR, and the model of 22.3% of the R factor was obtained in 8-2.4Å resolution. Three molecule half of a hexamer, i.e., subunits, is included in an unsymmetrical unit.

[0026]The bond form model was built using QUANTA on the guess computer graphics of the bond form model of example 8 EB-AP reaction intermediate and inosine (drawing 3). Molybdic acid was transposed to phosphoric acid as it was. Inosine was placed near the nucleoside portion of 5'-inosinic acid in the bond form model of wild type EB-AP and 5'-inosinic acid. However, although it is natural, since inosine does not have monoester phosphate combination, flexibility is higher [ inosine ] than making 5'-inosinic acid dock. Therefore, inosine tuned the position of inosine finely and considered it

as the bond form model so that it might combine with the molecule surface of EB-AP in the more desirable state. We decided to use this model for the design of subsequent enzyme variants.

[0027]Example 9 According to the model built in design example 8 of variant EB-AP which aimed at the improvement in compatibility with a nucleoside, a possibility that the side chain of Ser72 would interact with the base of inosine was suggested. When this residue was replaced by aromatic amino acid, such as phenylalanine, tyrosine, and tryptophan, the pi-pi interaction arose between the aromatic ring and the nucleoside base, and it was predicted that the compatibility over EB-AP of a nucleoside improves. Similarly, if it replaces by branched chain hydrophobic amino acid, such as valine, leucine, and isoleucine, When replaced by the amino acid which the CH/pi interaction arose between the branched chain hydrophobic group and the nucleoside base, and is tinged with negative charges, such as glutamic acid and aspartic acid, it paid well to the positive charge of a nucleoside base, and electrostatic, and improvement in compatibility was expected. Then, in order that phosphoryl-group-transfer activity may improve further the phosphoryl-group-transfer activity of relatively increasing G74 D/I153T variant EB-AP rather than phosphatase activity, We decided to produce S72F of this variant EB-AP, S72Y, S72W, S72V, S72E, and an S72D variant. We decided to also produce the variant which replaced S72 by other amino acid. Incidentally, these variants serve as 3 residue substitution variant EB-AP.

[0028]In order to build nine kinds of variant EB-AP for revealing Example 10Ser72 by production Escherichia coli JM109 of 3 residue substitution variant EB-AP replaced to other amino acid, Plasmid pEPI340 containing a G74 D/I153T variant EB-AP gene was used as a mold of the site-directed-mutagenesis method using PCR. pEPI340 is the plasmid which added the variation of G74 D/I 153T to plasmid pEPI305. A deer is carried out and the base sequence of these plasmids pEPI305 and pEPI340 is specified in Table 12 of the paragraph number (0143) of JP,10-201481,A. It is named AJ13144 and the international deposit of the stock which made plasmid pEPI305 hold to Escherichia coli JM109 is carried out to National Institute of Bioscience and Human-Technology, the Ministry of International Trade and Industry, as FERM BP-5423. [Refer to the paragraph number (0105) of the above-mentioned publication before examination - (0110) a statement.] Variation uses "a quick change site-directed-mutagenesis kit (Quickchange Site-Directed Mutagenesis Kit)" of Stratagene (Stratagene) (United States), and according to the protocol of the manufacturer, It introduced using the primer (drawing 7, array numbers 11-61 of an array table) corresponding to various enzyme variants. Escherichia coli XL-1 was transformed using the output of an PCR reaction. The transformed cell was smeared on L agar-medium plate containing 100 microl./ml ampicillin, and it incubated at 37 \*\* for 16 hours. The generated colony was extracted, and it cultivated, shaking overnight by L culture medium containing 100 microl./ml ampicillin. FlexiPrep Kit of Pharmacia Corp. (Sweden) was used after collecting biomasses by centrifugal separation from culture medium, and the plasmid was extracted according to the protocol of the manufacturer. The base sequence which encodes 3 residue substitution variant EB-AP in some numbers was checked by DNA sequence analysis. Composition of the primer set shown in drawing 7 was entrusted to Japanese Bio-Service.

[0029]Example 11 Escherichia coli JM109 which introduced the plasmid containing the phosphoryl-group-transfer activity of variant EB-AP and the measurement various 3 residue substitution variant EB-AP genes of a velocity constant was inoculated into 50 ml of L culture media containing 100 microl./ml ampicillin, and it cultivated at 37 \*\* for 16 hours. Biomasses were collected by centrifugal separation from culture medium, and it was suspended to 3 ml of 25mM phosphoric acid buffers (pH 7.0), and crushed by performing ultrasonication for 20 minutes at 4 \*\*. The treating solution was centrifuged and the cell-free extract was prepared except for the insoluble fraction. It checked by SDS-PAGE that each EB-AP3 residue substitution enzyme variant was revealed. The expression amount was about 20% of quality of total protein. The phosphoryl-group-transfer activity of the cell-free extract was measured on condition of the following. 2mM inosine, 100mM sodium pyrophosphate, a 100mM acetic acid buffer (pH 4.0), and the reaction mixture (1 ml) containing the cell-free extract of 100microl were incubated for 10 minutes at pH 4 and 30 \*\*. After adding 1N chloride 200mul and stopping a reaction, under [ a fixed quantity / inosinic acid / which was generated except for precipitate by centrifugal separation / 5'-]. The relative activity set to 1 showed 5'-inosinic acid generated amount when G74 D/I153T variant EB-AP which set phosphoryl-group-transfer activity of 3 residue substitution variant EB-AP as the object which introduces variation in some numbers was

used. Then,  $K_m$  value to the inosine in the phosphoryl-transfer reaction of 3 residue substitution variant EB-AP was measured on condition of the following in some numbers. The reaction mixture (1 ml) containing 100mM sodium pyrophosphate, a 100mM acetic acid buffer (pH 4.0), 10-100mM inosine, and the cell-free extract of 100microl was incubated for 10 minutes at pH 4 and 30 \*\*. After adding 1N chloride 200mul and stopping a reaction, under [ a fixed quantity / inosinic acid / which was generated except for precipitate by centrifugal separation / 5'-].  $K_m$  value was computed by Hanes-Woolf plot. A result is shown in Table 2.

[0030]

[Table 2]

	K <sub>m</sub> 値	リン酸転移活性
S72F/G74D/I153T	20mM	2.80
S72Y/G74D/I153T	25mM	2.04
S72W/G74D/I153T	30mM	1.71
S72D/G74D/I153T	33mM	1.59
S72V/G74D/I153T	40mM	2.46
S72E/G74D/I153T	40mM	3.19
S72M/G74D/I153T	46mM	1.94
S72T/G74D/I153T	50mM	1.91
S72L/G74D/I153T	57mM	2.24
S72R/G74D/I153T	59mM	1.99
S72Q/G74D/I153T	77mM	2.42
S72K/G74D/I153T	78mM	1.53
S72P/G74D/I153T	109mM	1.34
S72A/G74D/I153T	115mM	0.78
S72N/G74D/I153T	124mM	0.43
S72G/G74D/I153T	137mM	0.43
S72H/G74D/I153T	n. d.	n. d.
G74D/I153T	100mM	1.00
10残基置換変異型	40mM	1.44

[0031]  $K_m$  value to the inosine of all the variants (S72F, S72Y, S72W, S72V, S72L, S72E, S72D) predicted that compatibility with inosine will improve by the pi-pi interaction, the CH/pi interaction, and an electrostatic interaction in Example 9. It fell compared with the thing of G74 D/I153T variant EB-AP which does not carry out variation introduction, and the compatibility over inosine improved. Improvement was found also about phosphoryl-group-transfer activity. The variant of the improvement which introduced S72F especially was remarkable in  $K_m$  value, phosphoryl-group-transfer activity, and both sides. The aromatic ring and inosine base of phenylalanine carry out pi-pi interaction by suitable physical relationship, and it is surmised that improvement in compatibility was achieved.  $K_m$  value of S72M, S72T, R [ S72 ], S72Q, and S72K variant also fell. It is thought that some desirable interactions, such as a hydrophobic interaction and a hydrogen bond, arose between these amino acid residue and a nucleoside base. Incidentally, a gene was not able to be produced about S72I. Since there was a danger of making the mistaken SS linkage forming, S72C was not produced. High performance chromatography (HPLC) analyzed 5'-inosinic acid on condition of the following. column: -- Cosmosil 5C18-AR (4.6x150 mm) Nacalai Tesque, Inc. product mobile phase: -- 5mM potassium phosphate buffer (pH 2.8) / methanol =95/5 rate-of-flow: -- 1.0 ml/min temperature: -- room temperature detection: -- UV245nm [0032] Production G74 D/I153T variant of 5'-inosinic acid using Escherichia coli JM109 which introduced the example 12 S72 F/G74 D/I153T variant EB-AP gene, Escherichia coli JM109 which introduced the plasmid containing 10 residue substitution variant and an S72 F/G74 D/I153T variant EB-AP gene was inoculated into 50 ml of L culture media containing ampicillin 100microg/ml and IPTG 1mM, and it cultivated at 37 \*\* for 16 hours. 12 g/dl of pyrophoric acid and 6 g/dl of inosine are dissolved in an acetic acid buffer (pH 4.0). The reaction was performed at 30 \*\* for 24 hours, maintaining [ added the biomass of Escherichia coli JM109 which

introduced each of above-mentioned variant EB-AP genes into this so that it might become 100 mg/dl by dry cell weight, and ] pH to 4.0. The result of having measured the quantity of generated 5'-inosinic acid was shown in Table 3. As for the generated inosinic acid, the byproduction of 2'-inosinic acid and 3'-inosinic acid was not accepted at all only from 5'-inosinic acid. Although 7.5 g/dl of 5'-inosinic acid carried out generation accumulation at the reaction using Escherichia coli JM109 which introduced the plasmid containing a G74 D/I153T variant EB-AP gene, even if it developed reaction time, accumulation did not increase more than it. At the reaction using Escherichia coli JM109 which introduced the plasmid containing a 10 residue substitution variant EB-AP gene, accumulation improved and 5'-inosinic acid which is 12.1 g/dl carried out generation accumulation. It designed based on the spacial configuration, and at the reaction using Escherichia coli JM109 which introduced the plasmid containing the built S72 F/G74 D/I153T variant EB-AP gene, productivity improved further and 5'-inosinic acid which is 13.2 g/dl carried out generation accumulation.

[0033]

[Table 3]

導入した変異型酵素遺伝子	生成イノシン酸(g/dl)
G74D/I153T	7.5
10残基置換変異型	12.1
S72F/G74D/I153T	13.2

[0034] Measurement S72F variation of the phosphoryl-group-transfer activity of 3 residue substitution variant EB-AP and a velocity constant which introduced example 13 L16W, S71W, S73W, E104F, and E104W variation, Since it was thought that compatibility with inosine was raised by the pi-pi interaction, it searched for other amino acid residue which can plan a pi-pi interaction with an inosine base by substitution to aromatic ring amino acid on computer graphics. As a result, a possibility that the aromatic ring replaced by L16W, S71W, S73W, E104F, and E104W variation would interact with an inosine base was suggested. Then, a method which described these five sorts of 3 (G74 D/I153T variant EB-AP was used as base) residue substitution variant EB-AP in the Example 10 (the primer corresponding to each enzyme variant was shown in drawing 8.) It produced with the array numbers 62-76 of the array table, and phosphoryl-group-transfer activity and a velocity constant were measured by the method described in the Example 11. A result is shown in Table 4. Although phosphoryl-group-transfer activity fell also in which enzyme variant, Km value fell with all the enzyme variants, and it was suggested that the compatibility with inosine improved. Although Leu16 had separated 10A from Ser72 an interaction with inosine is predicted to be (in distance between C $\alpha$ ), even if separated to this extent, it was shown that an interaction with inosine is possible. Composition of the primer set shown in drawing 8 was entrusted to Japanese Bio-Service.

[0035]

[Table 4]

	K <sub>m</sub> 値	リン酸基転移活性
L16W/G74D/I153T	33mM	0.21
S71W/G74D/I153T	75mM	0.26
S73W/G74D/I153T	29mM	0.77
E104F/G74D/I153T	61mM	0.65
E104W/G74D/I153T	67mM	0.26
G74D/I153T	100mM	1.00
10残基置換変異型酵素	40mM	1.44

[0036] Example 14. In production EB-AP of 5'-inosinic acid using Escherichia coli JM109 which introduced production and this gene of the variant enzyme gene of Enterobacter aerogenes

(Enterobacter aerogenes) origin acid phosphatase (EA-AP). It was presupposed that a variation [ homologous / variation / three / of S72 F/G74 D/I 153T which raised the phosphoryl-group-transfer activity of inosine ] is introduced into EA-AP. The result of having aligned the amino acid sequence of EB-AP and EA-AP using the program BLAST is shown in drawing 9. It was shown that Ser72/Gly 74-/Ile153 of EB-AP corresponds to Ala70/Gly 72-/Ile151 in EA-AP. Then, A70 F/G72 D/I151T variant EA-AP was produced by the method described in the Example 10. It carried out using Escherichia coli JM109 which introduced the plasmid containing a variant enzyme gene by the method which described production of 5'-inosinic acid in the Example 12 from inosine. A result is shown in Table 5. A70 F/G72 D/I151T variant EA-AP showed 5'-inosinic acid productivity equivalent to S72 F/G74 D/I153T variant EB-AP.

[0037]

[Table 5]

導入した変異型酵素遺伝子	生成イノシン酸 (g/dl)
EA-AP A72F/G74D/I153T	13.1
EB-AP S72F/G74D/I153T	13.2

[0038] Drawing 9 is a figure showing the result of having performed amino acid sequence alignment of EB-AP and Enterobacter aerogenes origin acid phosphatase (EA-AP) by the program BLAST. The upper row is EB-AP and the lower berth is EA-AP. If it is similar amino acid residue even if the residue name is not the same, if both amino acid residue is the same, + will be displayed on the middle. The position of the 72nd residue (Ser72) of EB-AP was marked by [72]. Residue corresponding by EA-AP is Ala70.

[0039] Example 15 G72 D/I151T double mutant of MM-AP was crystallized using crystallization of Morganella MORUGANI origin acid phosphatase (MM-AP) origin G72 D/I151T enzyme variant, and steamy diffusion with a crystal-structure-analysis hanging drop method. The protein solution (concentration of 40mg/ml) concerned, and the polyethylene glycol 1000 of 25 (w/v %), 25mM ammonium sulfate, 125mM citrate buffer solution containing 25mM DTT (pH 4.8) an equivalent amount --- every (each 5microl). Carry out dropping mixing on the cover glass [ SHIRIKONAIZEISHON / cover glass ], and The polyethylene glycol 1000 of 25 (w/v %), 25mM ammonium sulfate, 125mM citrate buffer solution containing 25mM DTT (pH 4.8) It covered so that a mixed liquor drop might fish and fall on the well which filled 500microl, and it settled at 20 \*\*. The crystal deposited 2 or 3 days afterward, and, one week afterward, it grew up to be a measurable size (about 0.4x0.4x0.3 mm). Using X-ray diffractometer R-AXIS IIc of Rigaku, X diffraction data was collected and the crystallographic parameter was determined. The space group became P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> and the grating constant became a= 90.64 Å, b= 119.74 Å, and c= 136.14 Å. The diffraction data to 2.6Å resolution data was measured by 100K on Tsukuba and high energy research institute synchrotron radiation institution BL-6B. It was expected that estimate from the molecular weight of the volume of a unit cell, a space group, and an enzyme, and one molecule of a hexamer is contained in an unsymmetrical unit. Then, it analyzed with the molecular replacement method using the program amore by making hexamer structure of wild type EB-AP into a search model. In rotation search, the data of 10-4Å resolution was used for the data of 10-3Å resolution in translation search. The correct answer of both searches appeared as top peaks. After performing elaboration by using a molecule as a rigid body, it carried out by having repeated the structure correction on the graphics using QUANTA, and the structure refinement using X-PLOR, and the model of R factor 0.197 was obtained in 10-2.6Å resolution. The distance between Calpha atoms of five activity residue (Lys113, Arg120, His148, Arg181, His187) shown in drawing 1 was shown in Table 6. In MM-AP which is a relative enzyme of EB-AP, it was checked that all the interatomic distances between activity residue have fitted in the range specified from the spacial configuration of EB-AP.

[0040]

[Table 6]

		G74D/I153T 変異型EB-AP	下限	上限
Lys113	Arg120	11.3Å	10.4Å	12.6Å
	His148	12.6Å	11.3Å	13.8Å
	Arg181	16.3Å	14.5Å	17.4Å
	His187	12.5Å	10.7Å	13.6Å
Arg120	His148	14.0Å	12.2Å	15.2Å
	Arg181	10.9Å	9.4Å	11.8Å
	His187	6.1Å	4.5Å	6.7Å
His148	Arg181	8.9Å	6.7Å	9.8Å
	His187	10.2Å	8.8Å	11.0Å
Arg181	His187	5.4Å	4.5Å	6.8Å

[0041] In production of 10 residue substitution variant EB-AP which introduced example 16 A72F and A72E variation, and the measurement example 11 of phosphate transfer activity and a velocity constant, S72F to which Km value was reduced most, and the S72E variation which improved activity most were introduced into 10 residue substitution variant EB-AP. In 10 residue substitution variant EB-AP, since Ser72 is replaced by Ala, A72F and A72E variation will be introduced actually. If based on wild type EB-AP, 10 residue is replaced for both sides. A method which described these two sorts of variants in the Example 10 (the primer corresponding to each enzyme variant was shown in drawing 46.) It produced with the array numbers 77-82 of the array table. As a mold of the site-directed-mutagenesis method using PCR, plasmid pEMP370 (JP,9-37785,A, Example 19) containing a 10 residue substitution variant EB-AP gene was used. Phosphate transfer activity and a velocity constant were measured by the method described in the Example 11. A result is shown in Table 7. The relative activity which set 5'-inosinic acid generated amount when G74 D/I153T variant EB-AP was used to 1 showed phosphate transfer activity. Also in which enzyme variant, Km value fell notably. About phosphate transfer activity, it went up by A72E variation to having fallen by A72F variation.

[0042]

[Table 7]

	Km値	リン酸転移活性
A72F/10残基置換変異型酵素	9mM	0.11
A72E/10残基置換変異型酵素	15mM	2.30
10残基置換変異型酵素	40mM	1.44

[0043] Production A72F / 10 residue substitution variant EB-AP of 5'-inosinic acid using Escherichia coli JM109 which introduced example 17 A72F / 10 residue substitution variant EB-AP, and A72E / 10 residue substitution variant gene, and A72E / 10 residue substitution variant gene. The production experiment of 5'-inosinic acid using Escherichia coli JM109 which introduced the included plasmid was conducted by the method described in the Example 12. A result is shown in Table 8. The accumulated dose of 5'-inosinic acid increased both variants.

[0044]

[Table 8]

導入した変異型酵素遺伝子	生成イノシン酸 (g/dl)
A72F/10残基置換変異型	13.9
A72E/10残基置換変異型	13.9
10残基置換変異型	12.1

[0045] By measurement I103D variation of production of variant EB-AP which introduced example 18 I103D and T153N variation, phosphate transfer activity, and a velocity constant. It was suggested with the model of drawing 3 that replaced Asn forms the hydroxyl group and hydrogen bond of a ribose by that replaced Asp carries out an inosine base and an electrostatic interaction and T153N variation. Then, a method which introduced such residue into G74 D/I153T variant EB-AP, and described I103 D/G74 D/I153T variant EB-AP and G74 D/I153N variant EB-AP in the Example 10 (the primer corresponding to each enzyme variant was shown in drawing 47.) We decided to produce

with the array numbers 83-88 of an array table. Phosphate transfer activity and a velocity constant were measured by the method described in the Example 11. A result is shown in Table 9. The relative activity which set 5'-inosinic acid generated amount when G74 D/I153T variant EB-AP was used to 1 showed phosphate transfer activity. It was suggested that Km value fell and the compatibility of both variants with inosine improved although phosphoryl-group-transfer activity fell.

[0046]

[Table 9]

	Km値	リン酸転移活性
I103D/G74D/I153T	51mM	0.09
G74D/I153N	38mM	0.18
G74D/I153T	100mM	1.00

[0047]Although production of variant EB-AP which replaced Example 19Leu140 by Phe, Glu, and Lys, and measurement Leu140 of phosphate transfer activity and a velocity constant have separated not less than 10A from Ser72, they are located in the nearest to a phosphate bond part in the spacial configuration of a reaction intermediate analog. Therefore, when replacing this residue, the structure around a phosphate bond part in reaction intermediate changed, and it was thought by extension that influence also attained to the structure of a nucleoside binding site and fluctuation. If it replaces without Lys which has bulkier Phe and positive charge for this residue, and Glu which has a negative charge, it is hoped that compatibility with a nucleoside may change. Variation decided that phosphate transfer activity introduces into high A72E / 10 residue substitution product in Example 16. A method which described these three sorts of variants in the Example 10 (the primer corresponding to each enzyme variant was shown in drawing 4B.) It produced with the array numbers 89-97 of the array table. As a mold of the site-directed-mutagenesis method using PCR, the plasmid containing A72E / 10 residue substitution variant EB-AP gene was used. Phosphate transfer activity and a velocity constant were measured by the method described in the Example 11. A result is shown in Table 10. The relative activity which set 5'-inosinic acid generated amount when G74 D/I153T variant EB-AP was used to 1 showed phosphate transfer activity.

[0048]

[Table 10]

	Km値	リン酸転移活性
A72E/L140F/10残基置換変異型酵素	9mM	1.66
A72E/L140K/10残基置換変異型酵素	78mM	0.07
A72E/L140E/10残基置換変異型酵素	322mM	0.16
A72E/10残基置換変異型酵素	15mM	2.30

[0049]Km value fell [ the variant which introduced L140F ]. On the contrary, L140K and L140E variation raised Km substantially.

[0050]example 20 Enterobacter aerogenes . IFO. 12010 . Acid phosphatase of the Enterobacter aerogenes IFO12010 origin from the culture object of refining of origin wild type acid phosphatase and Escherichia coli JM109/pENP110 of example 24 statement of determination JP,10-201481,A of N-terminal-amino-acid arrangement. It refined, N-terminal-amino-acid arrangement was determined, and the amino acid sequence of maturation protein was determined. Escherichia coli JM109/pENP110 is the bacillus which introduced the acid phosphatase gene of the Enterobacter aerogenes IFO12010 origin into 109 shares of Escherichia coli JM, and produces this acid phosphatase. The amino acid sequence of the precursor protein expected from the base sequence of this acid phosphatase gene is arrangement shown in the array number 10 of an array table. 50 ml of nutrient media (pH 7.0) containing 1 g/dl of peptone, 0.5 g/dl of yeast extracts, and 1 g/dl of salt were put into a 500-ml Sakaguchi flask, and it heat-sterilized for 20 minutes at 120 \*\*. One platinum loop of Escherichia coli JM109/pENP110 was inoculated into this, and shaking culture was carried out at 30 \*\* for 16 hours. The biomass which collected biomasses from culture medium by centrifugal separation was suspended to the 100mM potassium phosphate buffer (pH 7.0) of 100 ml, ultrasonication was performed for 20 minutes at 4 \*\*, and the biomass was crushed. The treating solution was



centrifuged and the cell-free extract was prepared except for the insoluble fraction. Ammonium sulfate was added so that it might become this cell-free extract with saturation 30%. After removing the precipitate generated by centrifugal separation, additional addition of the ammonium sulfate was carried out so that it might become digestive liquor with saturation 60%. Centrifugal separation recovered the generated precipitate and it dissolved in the 100mM potassium phosphate buffer. After dialyzing this crude enzyme liquid 3 times to 500 ml of 100mM potassium phosphate buffers (pH 7.0), It charged in DEAE-TOYOPARU 650M column (phi3.0x10.0cm) equilibrated with 20mM potassium phosphate buffer (pH 7.0), and 20mM potassium phosphate buffer (pH 7.0) washed. Since phosphate transfer activity suited the bypassing fraction, the fractions concerned were collected. Ammonium sulfate was added so that it might become this activity fraction with saturation 35%, and this was made to stick to the butyl-Toyopearl column (phi3.0x7.0cm) equilibrated with 20mM potassium phosphate buffer (pH 7.0) which contains saturated ammonium sulfate 35%. This was eluted by the linear concentration gradient of the saturated potassium phosphate buffer (pH 7.0) 20% from saturation 35%. CM-TOYOPARU equilibrated with 10mM potassium phosphate buffer (pH 6.0) after collecting activity fractions and dialyzing to 10mM potassium phosphate buffer (pH 6.0) 1L. It was made to stick to a column (phi3.0x7.0cm). This was eluted by the linear concentration gradient of the potassium phosphate buffer (pH 6.0) containing 300mM potassium chloride from 0mM. These activity fractions were collected. The above operation refined the enzyme in which phosphate transfer activity is shown about 5 times with the recovery rate of about 16% more nearly eventually than a cell-free extract. This enzyme preparation was uniform in SDS-polyacrylamide electrophoresis. It is DITC about these refining enzymes. Membrane It is made to stick to [a milli gene / bio-search (Milligen/Biosearch) company make], When the amino acid sequence of the amino terminal was determined using Prosequencer 6625 (a milli gene / bio-search company make), the amino acid sequence of the amino terminal of 5 residue shown in the array number 98 of the array table was determined. Since the amino terminal of refining enzymes was started from the 21st alanine residue of the arrangement of the array number 10 of an array table, The amino acid sequence shown in the array number 10 of an array table is the arrangement of a precursor protein, and it was thought that peptide to the 20th phenylalanine residue was removed from the 1st methionine residue after translation. From this result, it was thought that the amino acid sequence of mature-bodies protein was arrangement shown in the amino acid numbers 1-228 during the arrangement shown in the array number 10 of an array table.

[0051]Example 21 *Enterobacter aerogenes* IFO 12010 High manifestation *Enterobacter aerogenes* of the enzyme by change of the promoter sequence of an origin new variant acid phosphatase gene IFO 12010 origin variant acid phosphatase. Site-specific mutation was introduced into the promotor arrangement part of the gene to encode with the gene engineering technique, and the gene which encodes the variant acid phosphatase which the enzyme expression amount increased was built. The gene which introduces variation used plasmid pENP170 built in Example 3 of the Japanese-Patent-Application-No. No. 189226 [ 12 to ] specification. This plasmid is *Enterobacter aerogenes*. The 1.6kbpDNA fragment cut down with the restriction enzyme SalI containing the gene which encodes IFO 12010 origin variant acid phosphatase, and the restriction enzyme KpnI, It is the plasmid DNA connected with pUC19 (made by TAKARA SHUZO CO., LTD.) cut by SalI and KpnI, and the base sequence of the SalI-KpnI 1.6kbpDNA fragment in pENP170 is arrangement shown in the array number 9 of an array table. The variation introduction to plasmid DNA used the Stratagene quick change site-directed-mutagenesis kit (Quick Change site-directed mutagenesis kit). Oligonucleotide MUT170 for variation introduction compounded using the DNA synthesizer (Applied Biosystem model 394) (array number 99 of an array table), Variation was introduced according to the protocol of Stratagene, using pENP170 as MUT171 (array number 100 of an array table), and a mold. *Escherichia coli* JM109 (made by TAKARA SHUZO CO., LTD.) was transformed with the conventional method using the obtained plasmid DNA. Plating of this was carried out on L agar medium containing 100 microg/ml ampicillin, and the transformant was obtained. It checked that prepared a plasmid by an alkali bacteriolysis method, determined a base sequence, and the target base was replaced from the transformant. Determination of a base sequence Taq DyeDeoxy Terminator Cycle Sequencing Kit (made by an applied biochemical company) is used, and it is the method of Sanger and others. It carried out according to [journal OBU leakage-at-bulb cue biology (J. Mol. Biol.), the 143rd volume,



and the 161st page (1980)]. It does in this way. *Enterobacter aerogenes* IFO. The variant gene which encodes the variant gene with which the base sequence of -10 field of the presumed promoter sequence located upstream of 12010 origin presumption acid phosphatase varied to the base sequence of the same TATAAT as the lac promoter of *Escherichia coli* from AAAAAT was built. The plasmid containing this variant gene was named pENP180.

[0052] *Escherichia coli* 50 ml of L culture media which contain ampicillin 100microg/ml for *Escherichia coli* JM109/pENP180 which introduced the gene which changed JM109/pENP170 and -10 field of the promoter sequence, And 50 ml of L culture media containing ampicillin 100microg/ml which added IPTG1mM were inoculated, respectively, and it cultivated at 37 \*\* for 16 hours. Biomasses were collected by centrifugal separation from the culture medium of each bacillus, and the physiological saline washed once. It was made to react at 30 \*\* for 1 hour, maintaining [ dissolve 15 g/dl of pyrophoric acid and inosine, and 8 g/dl in a 100mM acetic acid buffer (pH 4.0), add so that it may become 100 mg/dl by dry cell weight about each biomass at this, and ] pH to 4.0. The quantity of generated 5'-inosinic acid was shown in Table 11. High performance chromatography (HPLC) analyzed inosine and 5'-inosinic acid on condition of the following.

Column: Cosmosil 5C18-AR (4.6x150 mm) [Nacalai Tesque, Inc. products]

mobile phase: --- 5mM potassium phosphate buffer (pH 2.8) / methanol = 95/5 rate-of-flow: --- 1.0

ml/min temperature: --- room temperature detection: --- in UV245nm *Escherichia coli*

JM109/pENP170, although activity was low IPTG additive-free, Even if *Escherichia coli*

JM109/pENP180 did not add IPTG, it showed high activity. *Escherichia coli* JM109/pENP180 revealed still higher activity by adding IPTG, and it was shown that change of promoterregion is effective.

[0053]

[Table 11]

菌 株	IPTG	生成 5'-イノシン酸 (g/dl)
エシエリヒア・コリ JM109/pENP170	無添加	0. 7 3
	1 mM 添加	3. 0 9
エシエリヒア・コリ JM109/pENP180	無添加	2. 8 6
	1 mM 添加	3. 3 7

[0054] Example 22 *Enterobacter aerogenes* whose compatibility over a nucleoside improved IFO 12010 *Enterobacter aerogenes* built in construction example 21 of the origin new variant acid phosphatase gene IFO. Site-specific mutation was introduced into the 12010 origin variant acid phosphatase gene with the gene engineering technique, and the gene which encodes the variant acid phosphatase whose compatibility over a nucleoside, especially guanosine improved was produced. The substitution of amino acid residue was introduced combining the substitution of the amino acid residue identified contributing to the improvement in compatibility with a nucleoside based on the spacial configuration analysis of an *Escherichia BURATTAE* enzyme. The variation introduction to plasmid DNA used the Stratagene quick change site-directed-mutagenesis kit (Quick Change site-directed mutagenesis kit). 20 kinds of oligonucleotides for variation introduction from MUT180 (array number 101 of an array table) to MUT521 (array number 120 of an array table) were compounded using the DNA synthesizer (Applied Biosystem model 394). According to the protocol of Stratagene, variation was introduced as first mold, using MUT180 and MUT181 as pENP170 and an oligonucleotide for variation introduction. *Escherichia coli* JM109 (made by TAKARA SHUZO CO., LTD.) was transformed with the conventional method using the obtained plasmid DNA. Plating of this was carried out on L agar medium containing 100 microg/ml ampicillin, and the transformant was obtained. It checked that prepared a plasmid by an alkali bacteriolysis method, determined a base sequence, and the target base was replaced from the transformant. Determination of a base sequence In accordance with the method (the above-mentioned academic journal) of Sanger and others, it carried out using Taq DyeDeoxy Terminator Cycle Sequencing Kit (made by an applied biochemical company). Thus, the 153rd threonine residue (ACC) built the gene which encodes the variant acid phosphatase replaced by serine residue (TCC), and named pENP200 the plasmid containing this variant gene. The operation same as a new mold was repeated for the plasmid which introduced variation, and site-specific mutation was introduced

cumulatively. It checked that prepared a plasmid by an alkali bacteriolysis method, determined a base sequence, and the target base was replaced from the transformant. The variant enzyme gene and mutation site which encode the created variant acid phosphatase were shown in Table 12. The amino acid residue of the mutation site shows the amino acid residue in the amino acid sequence of the maturation protein shown in the array number 10 of the array table.

[0055] Each variant acid phosphatase gene. The included plasmid. introduced *Escherichia coli* . JM109/pENP180, *Escherichia coli* JM109/pENP320, *Escherichia coli* JM109/pENP340, *Escherichia coli* JM109/pENP410, *Escherichia coli* JM109/pENP510, And *Escherichia coli* JM109/pENP520 was inoculated into 50 ml of L culture media containing ampicillin 100microg/ml and IPTG1mM, and it cultivated at 37 \*\* for 16 hours. The biomass was suspended to a 50-ml 100mM phosphoric acid buffer (pH 7.0), ultrasonication was performed for 20 minutes at 4 \*\*, and the biomass was crushed. Biomasses were collected by centrifugal separation from the culture medium of each bacillus, and the physiological saline washed once. The treating solution was centrifuged and the cell-free extract was prepared except for the insoluble fraction. Km value to the inosine and guanosine in a phosphotransfer reaction was measured using each cell-free extract.

[0056] Measurement of the phosphate transfer activity to a nucleoside was performed by using inosine and guanosine as a substrate on the following conditions. pH 4.0 was performed by the reaction mixture (1 ml) containing the inosine or the guanosine, 100 micro a mol [/ml ] sodium pyrophosphate, the 100 micro mol/ml sodium acetate buffer solution (pH 4.0), and the enzyme of various concentration, and the reaction was performed at 30 \*\* for 10 minutes. After adding 2N chloride 200mul and suspending a reaction, under [ a fixed quantity / which was generated by the phosphotransfer reaction except for precipitate by centrifugal separation / 5'-inosinic acid or 5'-guanylic acid ]. High performance chromatography (HPLC) analyzed inosine, guanosine, 5'-inosinic acid, and 5'-guanylic acid on the same conditions as Example 21. The concentration of inosine or guanosine is changed on the reaction condition of the above-mentioned presentation, phosphate transfer activity is measured, and it is a Hanes-Woolf plot. It asked for the kinetic constant of the inosine in a phosphotransfer reaction, and guanosine by [a ZABAIO chemical journal (Biochem.J.), the 26th volume, and the 1406th page (1932)]. The result was shown in Table 13 - 16. It became clear that Km value to guanosine falls notably and the compatibility of Km value of the enzyme variant created in the example over guanosine is improving. Km value [ as opposed to inosine in four kinds of enzyme variants other than the enzyme variant by which a code is carried out to pENP520 ] was also falling dramatically.

[0057]

[Table 12]

配列の名称	配 番 号		長さ	配 列
MUT170	99	センス	30	5'-CTT ACA GAT GAC <u>TAT AAT</u> GTG ACT AAA AAC
MUT171	100	アンチセンス	30	5'-GTT TTT AGT CAC ATT ATA GTC ATC TGT AAG
MUT180	101	センス	33	5'-TCT ACC GGT TGG GCA <u>TCC</u> GCG CTG GTA CTG GCG
MUT181	102	アンチセンス	33	5'-CGC CAG TAC CAG CGC <u>GGA</u> TGC CCA ACC GGT AGA
MUT300	103	センス	33	5'-TCC GGC CAT ACC TCT <u>TCC</u> GGT TGG GCA TCC GCG
MUT301	104	アンチセンス	33	5'-CGC GGA TGC CCA ACC <u>GGA</u> AGA GGT ATG GCC GGA
MUT310	105	センス	33	5'-GAT GCT GAC CTG GCC <u>GTT</u> GGC GAC GTC GCG AAT
MUT311	106	アンチセンス	33	5'-ATT CGC GAC GTC GCC <u>AAC</u> GGC CAG GTC AGC ATC
MUT320	107	センス	33	5'-CTG ACA AAT ATG ATT <u>CTG</u> GAT GCC GGC GAT CTG
MUT321	108	アンチセンス	33	5'-CAG ATC GCC GGC ATC <u>CAG</u> AAT CAT ATT TGT CAG
MUT330	109	センス	33	5'-GAT GCT GAC CTG GCC <u>ATG</u> GGC GAC GTC GCG AAT
MUT331	110	アンチセンス	33	5'-ATT CGC GAC GTC GCC <u>CAT</u> GGC CAG GTC AGC ATC
MUT340	111	センス	33	5'-CTG ACA AAT ATG ATT <u>CAG</u> GAT GCC GGC GAT CTG
MUT341	112	アンチセンス	33	5'-CAG ATC GCC GGC ATC <u>CTG</u> AAT CAT ATT TGT CAG
MUT400	113	センス	33	5'-TCC GGC CAT ACC TCT <u>GCT</u> GGT TGG GCA TCC GCG
MUT401	114	アンチセンス	33	5'-CGC GGA TGC CCA ACC <u>AGC</u> AGA GGT ATG GCC GGA
MUT500	115	センス	33	5'-TCC GGC CAT ACC TCT <u>GGC</u> GGT TGG GCA TCC GCG
MUT501	116	アンチセンス	33	5'-CGC GGA TGC CCA ACC <u>GCC</u> AGA GGT ATG GCC GGA
MUT510	117	センス	33	5'-GAT GCT GAC CTG GCC <u>GAA</u> GGC GAC GTC GCG AAT
MUT511	118	アンチセンス	33	5'-ATT CGC GAC GTC GCC <u>TTC</u> GGC CAG GTC AGC ATC
MUT520	119	センス	33	5'-GAT GCT GAC CTG GCC <u>AAA</u> GGC GAC GTC GCG AAT
MUT521	120	アンチセンス	33	5'-ATT CGC GAC GTC GCC <u>TTT</u> GGC CAG GTC AGC ATC

[0058]

[Table 13]

プラスミド名	変異を導入したプラスミド	変異導入に用いたプライマー	変異点及びアミノ酸置換
pENP180			61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151I(ATC)→T(ACC)
pENP200	pENP130	MUT180, MUT181	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151T(ACC)→S(TCC)
pENP300	pENP200	MUT300, MUT301	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151I(ATC)→T(ACC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP310	pENP300	MUT310, MUT311	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→V(GTT) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151I(ATC)→T(ACC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP320	pENP310	MUT320, MUT321	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC)

[0059]

[Table 14]

			69S(AGC)→A(GCC) 70A(GCC)→V(GTT) 72G(GGC)→D(GAC) 102E(GAG)→L(CTG) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP330	pENP300	MUT330, MUT331	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→M(ATG) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP340	pENP330	MUT340, MUT341	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→V(GTT) 72G(GGC)→D(GAC) 102E(GAG)→Q(CAG) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP400	pENP200	MUT400, MUT401	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→A(GCT) 151T(ACC)→S(TCC)
pENP410	pENP400	MUT310, MUT311	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→V(GTT) 72G(GGC)→D(GAC)

[0060]

[Table 15]

			133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→A(GCT) 151T(ACC)→S(TCC)
pENP500	pENP200	MUT500, MUT501	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→G(GGC) 151T(ACC)→S(TCC)
pENP510	pENP500	MUT510, MUT511	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→E(GAA) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→G(GGC) 151T(ACC)→S(TCC)
pENP520	pENP500	MUT520, MUT521	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→K(AAA) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→G(GGC) 151T(ACC)→S(TCC)

[0061]

[Table 16]

	イノシンに対 する Km 値 (mM)	イノシンを基 質とした場合 の相対活性	グアノシンに 対する Km 値 (mM)	グアノシンを 基質とした時 の相対活性
pENP180	4.0	1.0	4.0	1.0
pENP320	1.9	1.9	4.6	1.5
pENP340	1.9	1.4	5.1	1.3
pENP410	1.8	1.0	4.9	0.70
pENP510	1.7	0.55	4.0	0.39
pENP520	4.6	0.63	4.4	0.21

[0062] Example 23 *Enterobacter aerogenes* whose compatibility over guanosine improved IFO 12010 the variant acid phosphatase gene of each phosphorylation of the guanosine by an origin new variant acid phosphatase transgenics bacillus. The included plasmid. introduced *Escherichia coli* . JM109/pENP180, *Escherichia coli* JM109/pENP320, *Escherichia coli* JM109/pENP340, *Escherichia coli* JM109/pENP410, *Escherichia coli* JM109/pENP510, And *Escherichia coli* JM109/pENP520 was inoculated into 50 ml of L culture media containing ampicillin 100microg/ml and IPTG1mM, and it cultivated at 37 \*\* for 16 hours. 10 g/dl of pyrophoric acid and 6.6 g/dl of grinding guanosine prepared like Example 1 of JP,12-189226,A are dissolved in a 100mM acetic acid buffer (pH 4.5), It

was made to react at 35 °C for 12 hours, maintaining [ to this, add each biomass so that it may become 100 mg/dl by dry cell weight, and ] pH to 4.5. The quantity of generated 5'-guanylic acid was shown in Table 17. Escherichia coli each whose bacillus which introduced the enzyme variant as shown in Table 17 is an old stock Productivity improved compared with JM109/pENP180, and generation accumulation of the 5'-guanylic acid was carried out with high yield.

[0063]

[Table 17]

菌 株	生成 5'-グアニル酸 (g/dl)
エシエリヒア・コリ JM109/pENP180	9.90
エシエリヒア・コリ JM109/pENP320	10.4
エシエリヒア・コリ JM109/pENP340	10.2
エシエリヒア・コリ JM109/pENP410	11.1
エシエリヒア・コリ JM109/pENP510	11.0
エシエリヒア・コリ JM109/pENP520	10.5

[0064]

[Effect of the Invention]As explained to details above, according to this invention, a variant nucleoside 5'-phosphoric acid production enzyme whose nucleoside 5'-phosphoric acid productivity improved, and a manufacturing method for the same are provided. According to this invention, the microorganism which holds the recombinant DNA which contains in the manufacturing method of nucleoside 5'-phosphoric acid the gene which encodes the useful aforementioned enzyme variant, and this gene, and this recombinant DNA is provided. It succeeded in the break through of the proteinic new spacial configuration by X ray crystal-structure-analysis art.

[0065]

[Layout Table]

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 Pro. Pro Pro Thr Ser Gly. Ser Pro Leu Gln Ala. His Asp Asp 50 55 60. Gln Thr Phe Asn Ser. Thr Arg  
 Gln Leu Lys. Gly Ser Thr Arg Trp Ala 65 70 75 80 Leu Ala Thr Gln Asp Ala Asp Leu His Leu Ala Ser  
 Val Leu Lys Asp 85 90 95 T. yr Ala Cys Ala Ala Gly. Met Asn Leu Asp Ile. Ala Gln Leu Pro His. 100  
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 Gln Ala Gly. Tyr Ile Met Ala Ser. Gly Glu Ile Ala Ala. 210 215 220 Leu His. Gly Asp Ala Asp Phe. Arg  
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tataacaccg taaggaaatg. tag atg aaa aag cgc. 355 Met Lys Lys Arg. -20 gtt ctc gcc etc. tgc etc gcc agc ctg. ttt tcc gtt aac gct. ttc ggc 403 Val Leu. Ala Leu Cys Leu Ala. Ser Leu Phe Ser Val. Asn Ala Phe Ala-15. -10 -5 -1ctg gtc cct. gcc ggc aat gat gca. acc acc aaa cgc gat. ctc tat tat 451 Leu. Val Pro Ala Gly Asn. Asp Ala Thr Thr Lys. Pro Asp Leu Tyr Tyr 1 5 10 15 ctg aaa aat gca cag gcc atc gat agt ctg ggc ctg ttg ccg ccg ccg 499 Leu Lys Asn Ala Gln Ala I. le Asp Ser Leu Ala Leu. Leu Pro Pro Pro 20 25. 30 ccg gaa gtt ggc agc. atc gca ttt tta aac. gat cag ggc atg tat. gag 547 Pro Glu Val. Gly Ser Ile Ala Phe. Leu Asn Asp Gln Ala. Met Tyr Glu 35 40 45. aaa gga cgg ctg ttg. cgc aat acc gaa cgt. ggc aag cag ggc cag. gca 595 Lys Gly Arg. Leu Leu Arg Asn Thr. Glu Arg Gly Lys Gln. Ala Gln Ala 50 55 60. gat gct gac ctg gcc. gcc ggc gac gtc ggc. aat gcc ttc tcc agc. gct 643 Asp Ala Asp Leu Ala Ala Gly Asp Val Ala Asn Ala Phe Ser Ser Ala 65 70 75 80ttt ggt tcg ccc atc acc ga. a aaa gac ggc ccg cag. tta cat aag ctg 691. Phe Gly Ser Pro Ile. Thr Glu Lys Asp Ala. Pro Gln Leu His Lys. Leu 85 90 95 ctg aca. aat atg att gag gat. gcc ggc gat ctg gcc. acc cgc agc ggc 739. Leu Thr Asn Met Ile. Glu Asp Ala Gly Asp. Leu Ala Thr Arg Ser. Ala 100 105 110 aaa. gag aaa tat atg cgc. att cgc ccg ttt ggc. ttc tac ggc gtt tca. 787 Lys Glu Lys Tyr. Met Arg Ile Arg Pro. Phe Ala Phe Tyr Gly. Val Ser 115 120 125 acc tgt aac act aaa gac cag gac aag ctg tcg aaa aac gga tct tac 835 Thr Cys Asn Thr Lys Asp Gln. Asp Lys Leu Ser Lys. Asn Gly Ser Tyr 130. 135 140 cct tcc ggc. cat acc tct acc ggt. tgg gca acc ggc ctg. gta ctg ggc 883 Pro. Ser Gly His Thr Ser. Thr Gly Trp Ala Thr. Ala Leu Val Leu Ala145. 150 155 160gag atc aat. ccg cag cgg caa aac. gaa att ctc aaa cgc. ggc tat gaa 931 Glu. Ile Asn Pro Gln Arg. Gln Asn Glu Ile Leu Lys Arg Gly Tyr Glu 165 170 175 ttg ggc gaa agc cgg gtt atc tgc ggc tat cat tgg cag agc gat gtc 979 Leu Gly Glu Ser Arg Val Ile Cys Gly Tyr. His Trp Gln Ser Asp. Val 180 185 190 gat. ggc ggc cgg ata gtc. ggc tcg ggc gtg gtg. ggc acc ctg cat acc. 1027 Asp Ala Ala Arg. Ile Val Gly Ser Ala. Val Val Ala Thr Leu. His Thr 195 200 205. aac ccg gcc ttc caa. cag cag ttg cag aaa. gca aag gat gaa ttc. gcc 1075 Asn Pro Ala. Phe Gln Gln Gln Leu. Gln Lys Ala Lys Asp. Glu Phe Ala 210 215. 220 aaa acg cag aag. taacgtcatc gccgttgaaac tcccggaggc ggcgcttaac 1127 Lys Thr Gln Lys 225 ggccttctc cgggtacta aatgcacag cgctgtagcc ccg. gtaagcg ccagcgccac 1187. cggggatttt gagatagcca. gcaccagtag ttccagccag. cgtgatgaat acattaacgg. 1247 caggccgcat gactgtaga. tactgttatc ggttgcaac. tttttaagg tttttcccg. 1307 gaggcggcgc gctgcgcctt. ctccgggcta ctaaatcgca. cagcgtgta gccccggtaa. 1367 gcggcagcgc caccgggggt. aacaagcgca gattcagaag. cgcgtgacga acggcgcggt. 1427 atccgggcgc gtaaacaatgg. ttgatgcttt taactgcggc. gtgccaaggt agaggaaacc. 1487 gacaattttg tctgttcgc. ggcagccaaa gccttcgcgg acaaccggac tctcggttaa 1547 cgcaccgata cgccagatac cgttatagcc ctgcgcact gcggc. cattt gcacgccat 1607 caccgcacat cccgcggaca tctcctgttc ccacagcggt acc 1650[0075]

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 10

[Translation done.]



## \* NOTICES \*

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- 2.\*\*\*\* shows the word which can not be translated.
- 3.In the drawings, any words are not translated.

## DESCRIPTION OF DRAWINGS

### [Brief Description of the Drawings]

[Drawing 1]It is a figure showing these space position relations with five amino acid residue used as the component of the active site which has phosphatase activity or phosphoryl-group-transfer activity as a distance between Calpha atoms.

[Drawing 2]It is the figure which aligned the amino acid sequence of EB-AP with the amino acid sequence of Morganella MORUGANI, Salmonella typhimurium, and ZAIMO monas MOBIRISU origin acid phosphatase.

[Drawing 3]It is a photograph of the computer graphics (CG) which shows the crystal structure of the bond form model of an EB-AP reaction intermediate analog and inosine.

[Drawing 4]It is a photograph of CG which shows the crystal structure of the hexamer molecule of EB-AP.

[Drawing 5]It is a photograph of CG which shows the crystal structure of the subunit of EB-AP.

[Drawing 6]It is a figure showing the active site architecture of EB-AP.

[Drawing 7]It is a figure showing the primer set used for the site-directed-mutagenesis method.

[Drawing 8]It is a figure showing the primer set used for the site-directed-mutagenesis method.

[Drawing 9]It is a figure showing the result of having performed amino acid sequence alignment of EB-AP and Enterobacter aerogenes origin acid phosphatase (EA-AP) by the program BLAST.

[Drawing 10]It is a figure showing the crystallography data (1) of the structure of EB-AP.

[Drawing 11]It is a figure showing the crystallography data (2) of the structure of EB-AP.

[Drawing 12]It is a figure showing the crystallography data (3) of the structure of EB-AP.

[Drawing 13]It is a figure showing the crystallography data (4) of the structure of EB-AP.

[Drawing 14]It is a figure showing the crystallography data (5) of the structure of EB-AP.

[Drawing 15]It is a figure showing the crystallography data (6) of the structure of EB-AP.

[Drawing 16]It is a figure showing the crystallography data (7) of the structure of EB-AP.

[Drawing 17]It is a figure showing the crystallography data (8) of the structure of EB-AP.

[Drawing 18]It is a figure showing the crystallography data (9) of the structure of EB-AP.

[Drawing 19]It is a figure showing the crystallography data (10) of the structure of EB-AP.

[Drawing 20]It is a figure showing the crystallography data (11) of the structure of EB-AP.

[Drawing 21]It is a figure showing the crystallography data (12) of the structure of EB-AP.

[Drawing 22]It is a figure showing the crystallography data (13) of the structure of EB-AP.

[Drawing 23]It is a figure showing the crystallography data (14) of the structure of EB-AP.

[Drawing 24]It is a figure showing the crystallography data (15) of the structure of EB-AP.

[Drawing 25]It is a figure showing the crystallography data (16) of the structure of EB-AP.

[Drawing 26]It is a figure showing the crystallography data (17) of the structure of EB-AP.

[Drawing 27]It is a figure showing the crystallography data (18) of the structure of EB-AP.

[Drawing 28]It is a figure showing the crystallography data (19) of the structure of EB-AP.

[Drawing 29]It is a figure showing the crystallography data (20) of the structure of EB-AP.

[Drawing 30]It is a figure showing the crystallography data (21) of the structure of EB-AP.

[Drawing 31]It is a figure showing the crystallography data (22) of the structure of EB-AP.

[Drawing 32]It is a figure showing the crystallography data (23) of the structure of EB-AP.

[Drawing 33]It is a figure showing the crystallography data (24) of the structure of EB-AP.

[Drawing 34] It is a figure showing the crystallography data (25) of the structure of EB-AP.  
[Drawing 35] It is a figure showing the crystallography data (26) of the structure of EB-AP.  
[Drawing 36] It is a figure showing the crystallography data (27) of the structure of EB-AP.  
[Drawing 37] It is a figure showing the crystallography data (28) of the structure of EB-AP.  
[Drawing 38] It is a figure showing the crystallography data (29) of the structure of EB-AP.  
[Drawing 39] It is a figure showing the crystallography data (30) of the structure of EB-AP.  
[Drawing 40] It is a figure showing the crystallography data (31) of the structure of EB-AP.  
[Drawing 41] It is a figure showing the crystallography data (32) of the structure of EB-AP.  
[Drawing 42] It is a figure showing the crystallography data (33) of the structure of EB-AP.  
[Drawing 43] It is a figure showing the crystallography data (34) of the structure of EB-AP.  
[Drawing 44] It is a figure showing the crystallography data (35) of the structure of EB-AP.  
[Drawing 45] It is a figure showing the crystallography data (36) of the structure of EB-AP.  
[Drawing 46] It is a figure showing the primer set used for the site-directed-mutagenesis method.  
[Drawing 47] It is a figure showing the primer set used for the site-directed-mutagenesis method.  
[Drawing 48] It is a figure showing the primer set used for the site-directed-mutagenesis method.

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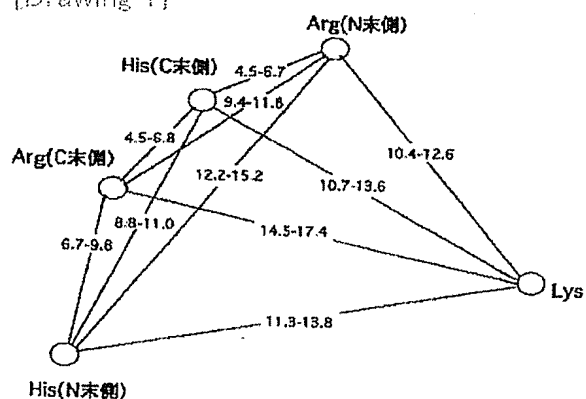
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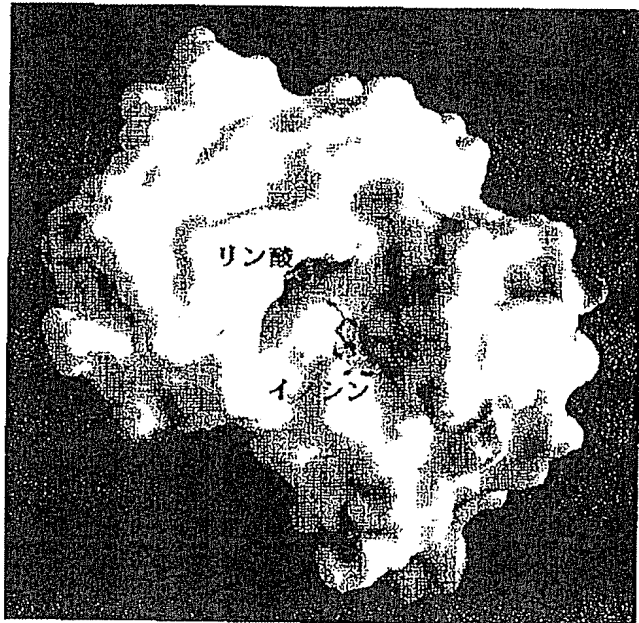
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## DRAWINGS

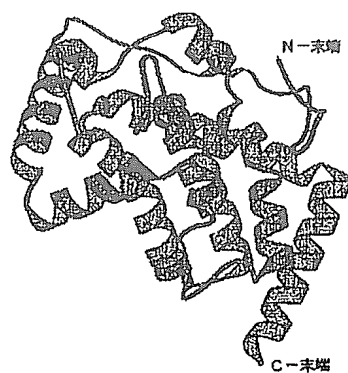
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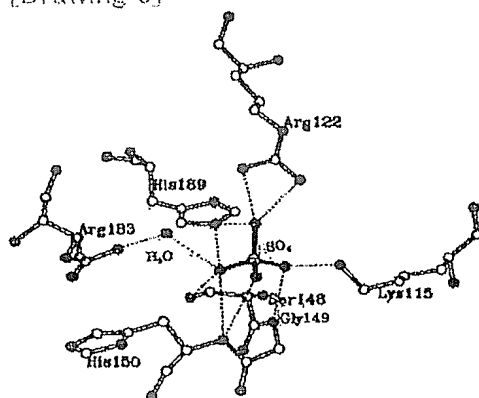
[Drawing 3]



[Drawing 5]



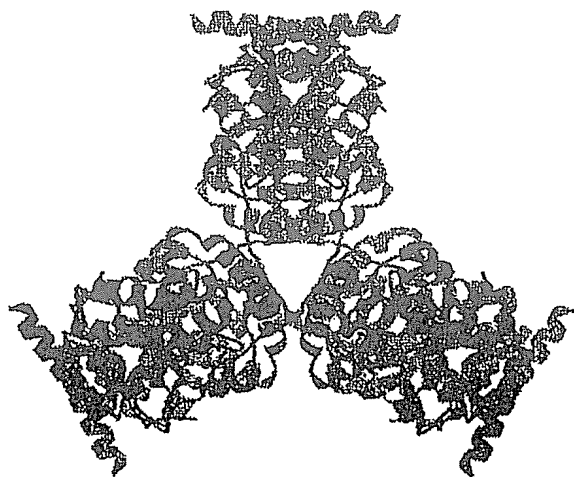
[Drawing 6]



[Drawing 2]

	$\alpha 1$	$\alpha 2$	$\alpha 3$
<i>E. blattae</i>	:LALVATGNDT	TTKPDLYLX NSEAINSLAL	LPPPPAVGSI AFLNDQAMYE QGRLRNTER GKLAEDANL 70
<i>M. morganii</i>	: AIPAGNDA	TTKPDLYLX NEQALDSLKL	LPPPPFVGS I QFLNDQAMYE KGRMLRNTER GKQAOQADADL
<i>S. typhimurium</i>	: KYT	SAETVQPFHS PEESVNSQFY	LPPPPGNDDE AYRYDKEAYF KGYAILGSPR WKQAAEDADV
<i>Z. mobilis</i>	:ASGLSQSVSA	HTEKSEPSST YHFHSDPLLY	LAPPPISGSP LQAHHDDQTFN STRQLKGSSTR WALATQDADL * **
	$\alpha 4$	$\alpha 5$	$\alpha 6$
<i>E. blattae</i>	:SSGGVANAFS	GAFGSPITEK	DAPALHKLIT NMIEDAGDLA
<i>M. morganii</i>	:AAGGVATAFS	GAFGYPITEK	DSPELYKLIT NMIEDAGDLA
<i>S. typhimurium</i>	:SVENIARIFS	PVVGAKINPK	DTPETWNMLK NLLTMGGYFA
<i>Z. mobilis</i>	:HLASVLKDYA	CAAGMNLIDIA *	QLPHLANLIK RALRTEYDDI GR-AKNNMNR KREFVDTDQP ICTEKDREGI * *
	$\alpha 7$	$\alpha 8$	$\alpha 9$
<i>E. blattae</i>	:SSGGVANAFS	GAFGSPITEK	DAPALHKLIT NMIEDAGDLA
<i>M. morganii</i>	:AAGGVATAFS	GAFGYPITEK	DSPELYKLIT NMIEDAGDLA
<i>S. typhimurium</i>	:SVENIARIFS	PVVGAKINPK	DTPETWNMLK NLLTMGGYFA
<i>Z. mobilis</i>	:HLASVLKDYA	CAAGMNLIDIA *	QLPHLANLIK RALRTEYDDI GR-AKNNMNR KREFVDTDQP ICTEKDREGI * *
	$\alpha 10$	$\alpha 11$	$\alpha 12$
<i>E. blattae</i>	:SKNGSYPSGH	TSIGWATALV	LAENPQRON EILKRGYELG
<i>M. morganii</i>	:STNGSYPSGH	TSIGWATALV	LAEVNEANOD AILERGYQLG
<i>S. typhimurium</i>	:RKNGSYPSGH	TAYGTLLALV	LSEARPERAQ ELARRGWEEG
<i>Z. mobilis</i>	:GKQGSYPSGH	TTIGWSVALI	LAELIPDHAA NILQRQIIFG
	*****	* * *	* * *
	$\alpha 13$		
<i>E. blattae</i>	:NPAFOQLOK	AKAEFAQHOK	K
<i>M. morganii</i>	:DPAFOQLOK	AKQEFQKSK	K
<i>S. typhimurium</i>	:IPAFQKSLAK	VREELNDKNN	LLSKEDHPKL NY
<i>Z. mobilis</i>	:DADFRDMEL	ARKELEKART	SAHTPDDLJC KIEQSAR *

[Drawing 4]



[Drawing 7]

S72F(s) 5'-CA-AAC-CTG-AGC-TTT-GGC-GAT-GTG-GC-3'  
 S72F(as) 3'-GT-TTG-GAC-TCG-AAA-CCG-CTA-CAC-CG-5'  
           N L S F72 G D V  
 S72Y(s) 5'-CA-AAC-CTG-AGC-TAC-GGC-GAT-GTG-GC-3'  
 S72Y(as) 3'-GT-TTG-GAC-TCG-ATG-CCG-CTA-CAC-CG-5'  
           N L S Y72 G D V  
 S72W(s) 5'-CA-AAC-CTG-AGC-TGG-GGC-GAT-GTG-GC-3'  
 S72W(as) 3'-GT-TTG-GAC-TCG-ACC-CCG-CTA-CAC-CG-5'  
           N L S W72 G D V  
 S72D(s) 5'-CA-AAC-CTG-AGC-GAC-GGC-GAT-GTG-GC-3'  
 S72D(as) 3'-GT-TTG-GAC-TCG-CTG-CCG-CTA-CAC-CG-5'  
           N L S D72 G D V  
 S72V(s) 5'-CA-AAC-CTG-AGC-GTT-GGC-GAT-GTG-GC-3'  
 S72V(as) 3'-GT-TTG-GAC-TCG-CAA-CCG-CTA-CAC-CG-5'  
           N L S V72 G D V  
 S72E(s) 5'-CA-AAC-CTG-AGC-GAA-GGC-GAT-GTG-GC-3'  
 S72E(as) 3'-GT-TTG-GAC-TCG-CTT-CCG-CTA-CAC-CG-5'  
           N L S E72 G D V  
 S72M(s) 5'-CA-AAC-CTG-AGC-ATG-GGC-GAT-GTG-GC-3'  
 S72M(as) 3'-GT-TTG-GAC-TCG-TAC-CCG-CTA-CAC-CG-5'  
           N L S M72 G D V  
 S72T(s) 5'-CA-AAC-CTG-AGC-ACC-GGC-GAT-GTG-GC-3'  
 S72T(as) 3'-GT-TTG-GAC-TCG-TGG-CCG-CTA-CAC-CG-5'  
           N L S T72 G D V  
 S72L(s) 5'-CA-AAC-CTG-AGC-CTG-GGC-GAT-GTG-GC-3'  
 S72L(as) 3'-GT-TTG-GAC-TCG-GAC-CCG-CTA-CAC-CG-5'  
           N L S L72 G D V  
 S72R(s) 5'-CA-AAC-CTG-AGC-CGT-GGC-GAT-GTG-GC-3'  
 S72R(as) 3'-GT-TTG-GAC-TCG-GCA-CCG-CTA-CAC-CG-5'  
           N L S R72 G D V  
 S72Q(s) 5'-CA-AAC-CTG-AGC-CAG-GGC-GAT-GTG-GC-3'  
 S72Q(as) 3'-GT-TTG-GAC-TCG-GTC-CCG-CTA-CAC-CG-5'  
           N L S Q72 G D V  
 S72K(s) 5'-CA-AAC-CTG-AGC-AAA-GGC-GAT-GTG-GC-3'  
 S72K(as) 3'-GT-TTG-GAC-TCG-TTT-CCG-CTA-CAC-CG-5'  
           N L S K72 G D V  
 S72P(s) 5'-CA-AAC-CTG-AGC-CCG-GGC-GAT-GTG-GC-3'  
 S72P(as) 3'-GT-TTG-GAC-TCG-GGC-CCG-CTA-CAC-CG-5'  
           N L S P72 G D V  
 S72A(s) 5'-CA-AAC-CTG-AGC-GCG-GGC-GAT-GTG-GC-3'  
 S72A(as) 3'-GT-TTG-GAC-TCG-CGC-CCG-CTA-CAC-CG-5'  
           N L S A72 G D V  
 S72N(s) 5'-CA-AAC-CTG-AGC-AAC-GGC-GAT-GTG-GC-3'  
 S72N(as) 3'-GT-TTG-GAC-TCG-TTG-CCG-CTA-CAC-CG-5'  
           N L S N72 G D V  
 S72G(s) 5'-CA-AAC-CTG-AGC-GGT-GGC-GAT-GTG-GC-3'  
 S72G(as) 3'-GT-TTG-GAC-TCG-CCA-CCG-CTA-CAC-CG-5'  
           N L S G72 G D V  
 S72H(s) 5'-CA-AAC-CTG-AGC-CAC-GGC-GAT-GTG-GC-3'  
 S72H(as) 3'-GT-TTG-GAC-TCG-GTG-CCG-CTA-CAC-CG-5'  
           N L S H72 G D V

[Drawing 8]

L16W(s) 5' -CG-AAA-CCG-GAT-TGG-TAC-TAC-CTC-AA-3'  
 L16W(as) 3' -GC-TTT-GGC-CTA-ACC-ATG-ATG-GAG-TT-5'  
           K    P    D    W16 Y    Y    L

S71W(s) 5' -AT-GCA-AAC-CTG-TGG-AGT-GGC-GAT-GT-3'  
 S71W(as) 3' -TA-CGT-TTG-GAC-ACC-TCA-CCG-CTA-CA-5'  
           A    N    L    W71 S    G    D

G73W(s) 5' -AC-CTG-AGC-AGT-TGG-GAT-GTG-GCG-AA-3'  
 G73W(as) 3' -TG-GAC-TCG-TCA-ACC-CTA-CAC-CGC-TT-5'  
           L    S    S    W73 D    V    A

E104F(s) 5' -CC-AAT-ATG-ATT-TTT-GAC-GCC-GGG-GA-3'  
 E104F(as) 3' -GG-TTA-TAC-TAA-AAA-CTG-CGG-CCC-CT-5'  
           N    M    I    F104 D    A    G

E104W(s) 5' -CC-AAT-ATG-ATT-TGG-GAC-GCC-GGG-GA-3'  
 E104W(as) 3' -GG-TTA-TAC-TAA-ACC-CTG-CGG-CCC-CT-5'  
           N    M    I    W104 D    A    G

[Drawing 9]

EB-AP: LALVATGNDTTTKPDLYYLKNSEAINSLALLPPPPAVGSIAFLNDQAMYEQGRLLRNTER  
           V    GND TTKPDLYYLKN++AI+SLALLPPPP VGSIAFLNDQAMYE+GRLLRNTER  
 EA-AP: LVPAGNDATTKPDLYYLKNAQAIDSLALLPPPPEVGSIAFLNDQAMYEKGRLLRNTER

[72]

EB-AP: GKLAEDANLSSGGVANAFSGAFGSPITEKDAPALHKLLTNMIEDAGDLATRSKDHMYR  
           GKLAEDANLS+GGVANAFS AFGSPITEKDAP LHKLLTNMIEDAGDLATRSK+ YMR  
 EA-AP: GKLAEDANLSAGGVANAFSSAFGSPITEKDAPQLHKLLTNMIEDAGDLATRSKEKYMR

[70]

EB-AP: IRPFAFYGVSTCNTTEQDKLSKNGSYPSGHTSIGWATALVLAIEINPQRQNEILKRGYELG  
           IRPFAFYGVSTCNTTEQDKLSKNGSYPSGHTSIGWATALVLAIEINPQRQNEILKRGYELG  
 EA-AP: IRPFAFYGVSTCNTTEQDKLSKNGSYPSGHTSIGWATALVLAIEINPQRQNEILKRGYELG

EB-AP: QSRVICGYHWQSDVDAAARVVGSVAVATLHTNPFAFQQQLQKAKAEFAQHOKK  
           +SRVICGYHWQSDVDAAAR+VGSVAVATLHTNPFAFQQQLQKAK EFA+ QK  
 EA-AP: ESRVICGYHWQSDVDAAARIVGSVAVATLHTNPFAFQQQLQKAKDEFKTOK

[Drawing 10]



ATOM	1	N	GLY	A	7	35.965	71.208	89.712	1.00	36.57
ATOM	2	CA	GLY	A	7	37.459	71.295	89.574	1.00	31.92
ATOM	3	C	GLY	A	7	38.160	69.982	89.872	1.00	29.76
ATOM	4	O	GLY	A	7	39.301	69.858	89.492	1.00	31.81
ATOM	5	N	ASN	A	8	37.485	68.990	90.532	1.00	26.40
ATOM	6	CA	ASN	A	8	38.284	67.775	90.697	1.00	26.63
ATOM	7	C	ASN	A	8	38.466	67.018	89.396	1.00	29.21
ATOM	8	O	ASN	A	8	37.736	67.238	88.431	1.00	30.52
ATOM	9	CB	ASN	A	8	37.677	66.810	91.702	1.00	27.01
ATOM	10	CG	ASN	A	8	37.725	67.396	93.104	1.00	32.45
ATOM	11	OD1	ASN	A	8	38.751	67.744	93.636	1.00	30.02
ATOM	12	ND2	ASN	A	8	36.545	67.536	93.707	1.00	31.60
ATOM	13	N	ASP	A	9	39.455	66.154	89.463	1.00	29.14
ATOM	14	CA	ASP	A	9	39.787	65.216	88.391	1.00	30.47
ATOM	15	C	ASP	A	9	40.661	64.081	88.901	1.00	31.02
ATOM	16	O	ASP	A	9	40.804	63.931	90.110	1.00	31.00
ATOM	17	CB	ASP	A	9	40.394	65.960	87.195	1.00	30.92
ATOM	18	CG	ASP	A	9	41.802	66.484	87.429	1.00	32.66
ATOM	19	OD1	ASP	A	9	42.307	66.333	88.532	1.00	35.03
ATOM	20	OD2	ASP	A	9	42.400	67.018	86.493	1.00	31.63
ATOM	21	N	THR	A	10	41.272	63.298	87.998	1.00	28.72
ATOM	22	CA	THR	A	10	42.188	62.228	88.430	1.00	28.53
ATOM	23	C	THR	A	10	43.408	62.655	89.259	1.00	30.10
ATOM	24	O	THR	A	10	43.946	61.944	90.095	1.00	29.06
ATOM	25	CB	THR	A	10	42.692	61.405	87.235	1.00	26.05
ATOM	26	OG1	THR	A	10	43.272	60.172	87.655	1.00	27.75
ATOM	27	CG2	THR	A	10	43.670	62.174	86.313	1.00	23.76
ATOM	28	N	THR	A	11	43.814	63.900	88.996	1.00	30.82
ATOM	29	CA	THR	A	11	44.932	64.389	89.799	1.00	32.79
ATOM	30	C	THR	A	11	44.605	64.736	91.267	1.00	36.32
ATOM	31	O	THR	A	11	45.435	64.658	92.162	1.00	37.21
ATOM	32	CB	THR	A	11	45.588	65.591	89.143	1.00	30.53
ATOM	33	OG1	THR	A	11	44.845	66.781	89.359	1.00	27.79
ATOM	34	CG2	THR	A	11	45.899	65.362	87.656	1.00	32.16
ATOM	35	N	THR	A	12	43.317	65.076	91.495	1.00	34.81
ATOM	36	CA	THR	A	12	42.910	65.213	92.900	1.00	32.91
ATOM	37	C	THR	A	12	42.265	63.992	93.549	1.00	33.08
ATOM	38	O	THR	A	12	42.350	63.742	94.736	1.00	32.49
ATOM	39	CB	THR	A	12	41.963	66.395	93.077	1.00	30.92
ATOM	40	OG1	THR	A	12	40.719	66.162	92.409	1.00	32.04
ATOM	41	CG2	THR	A	12	42.599	67.667	92.543	1.00	29.75
ATOM	42	N	LYS	A	13	41.565	63.229	92.703	1.00	31.17
ATOM	43	CA	LYS	A	13	40.791	62.064	93.174	1.00	30.27
ATOM	44	C	LYS	A	13	40.904	60.812	92.287	1.00	31.40
ATOM	45	O	LYS	A	13	39.981	60.348	91.605	1.00	33.05
ATOM	46	CB	LYS	A	13	39.294	62.395	93.331	1.00	29.09
ATOM	47	CG	LYS	A	13	39.001	63.747	93.965	1.00	32.97
ATOM	48	CD	LYS	A	13	37.536	64.076	94.166	1.00	37.86
ATOM	49	CE	LYS	A	13	36.767	62.909	94.772	1.00	47.28
ATOM	50	NZ	LYS	A	13	35.340	63.270	94.947	1.00	52.08
ATOM	51	N	PRO	A	14	42.138	60.283	92.279	1.00	33.01
ATOM	52	CA	PRO	A	14	42.516	59.249	91.290	1.00	32.06
ATOM	53	C	PRO	A	14	41.823	57.907	91.452	1.00	30.98
ATOM	54	O	PRO	A	14	41.961	56.989	90.668	1.00	32.57

[Drawing 11]

ATOM	55	CB	PRO	A	14	44.035	59.145	91.468	1.00	34.46
ATOM	56	CG	PRO	A	14	44.283	59.564	92.920	1.00	33.02
ATOM	57	CD	PRO	A	14	43.225	60.638	93.181	1.00	34.46
ATOM	58	N	ASP	A	15	41.046	57.815	92.513	1.00	29.27
ATOM	59	CA	ASP	A	15	40.204	56.655	92.809	1.00	28.89
ATOM	60	C	ASP	A	15	38.810	56.684	92.146	1.00	21.76
ATOM	61	O	ASP	A	15	38.078	55.706	92.030	1.00	20.59
ATOM	62	CB	ASP	A	15	40.125	56.599	94.368	1.00	37.60
ATOM	63	CG	ASP	A	15	39.589	57.903	95.080	1.00	45.11
ATOM	64	OD1	ASP	A	15	40.062	59.044	94.817	1.00	45.67
ATOM	65	OD2	ASP	A	15	38.687	57.751	95.922	1.00	49.07
ATOM	66	N	LEU	A	16	38.495	57.910	91.726	1.00	20.49
ATOM	67	CA	LEU	A	16	37.182	58.179	91.135	1.00	23.90
ATOM	68	C	LEU	A	16	37.156	58.814	89.727	1.00	22.23
ATOM	69	O	LEU	A	16	36.109	59.011	89.134	1.00	23.21
ATOM	70	CB	LEU	A	16	36.354	59.099	92.029	1.00	23.35
ATOM	71	CG	LEU	A	16	35.814	58.432	93.297	1.00	25.48
ATOM	72	CD1	LEU	A	16	34.876	57.253	93.075	1.00	24.05
ATOM	73	CD2	LEU	A	16	35.092	59.477	94.104	1.00	25.22
ATOM	74	N	TYR	A	17	38.343	59.175	89.273	1.00	20.96
ATOM	75	CA	TYR	A	17	38.555	59.605	87.889	1.00	22.04
ATOM	76	C	TYR	A	17	39.780	58.903	87.334	1.00	22.80
ATOM	77	O	TYR	A	17	40.790	58.799	88.021	1.00	23.48
ATOM	78	CB	TYR	A	17	38.856	61.095	87.711	1.00	18.01
ATOM	79	CG	TYR	A	17	37.928	62.099	88.371	1.00	24.78
ATOM	80	CD1	TYR	A	17	37.129	62.916	87.542	1.00	22.78
ATOM	81	CD2	TYR	A	17	37.905	62.248	89.781	1.00	23.58
ATOM	82	CE1	TYR	A	17	36.317	63.919	88.113	1.00	26.51
ATOM	83	CE2	TYR	A	17	37.090	63.240	90.349	1.00	22.88
ATOM	84	CZ	TYR	A	17	36.303	64.059	89.517	1.00	24.63
ATOM	85	OH	TYR	A	17	35.482	65.023	90.066	1.00	22.92
ATOM	86	N	TYR	A	18	39.670	58.482	86.053	1.00	26.17
ATOM	87	CA	TYR	A	18	40.838	58.209	85.191	1.00	21.13
ATOM	88	C	TYR	A	18	41.332	59.414	84.464	1.00	19.92
ATOM	89	O	TYR	A	18	42.490	59.511	84.083	1.00	22.64
ATOM	90	CB	TYR	A	18	40.563	57.195	84.080	1.00	17.53
ATOM	91	CG	TYR	A	18	40.312	55.826	84.610	1.00	16.91
ATOM	92	CD1	TYR	A	18	41.425	55.028	84.916	1.00	19.86
ATOM	93	CD2	TYR	A	18	38.985	55.372	84.771	1.00	16.65
ATOM	94	CE1	TYR	A	18	41.218	53.725	85.383	1.00	18.64
ATOM	95	CE2	TYR	A	18	38.765	54.053	85.213	1.00	17.52
ATOM	96	CZ	TYR	A	18	39.892	53.262	85.515	1.00	21.18
ATOM	97	OH	TYR	A	18	39.734	51.974	85.977	1.00	26.15
ATOM	98	N	LEU	A	19	40.412	60.336	84.236	1.00	21.49
ATOM	99	CA	LEU	A	19	40.788	61.462	83.366	1.00	22.71
ATOM	100	C	LEU	A	19	41.094	62.812	84.021	1.00	25.01
ATOM	101	O	LEU	A	19	40.771	63.125	85.159	1.00	25.24
ATOM	102	CB	LEU	A	19	39.708	61.669	82.290	1.00	21.68
ATOM	103	CG	LEU	A	19	39.301	60.442	81.432	1.00	22.88
ATOM	104	CD1	LEU	A	19	40.430	59.842	80.583	1.00	20.39
ATOM	105	CD2	LEU	A	19	38.078	60.812	80.608	1.00	18.83
ATOM	106	N	LYS	A	20	41.736	63.667	83.246	1.00	26.44
ATOM	107	CA	LYS	A	20	41.947	65.032	83.717	1.00	26.77
ATOM	108	C	LYS	A	20	40.935	66.034	83.292	1.00	26.42

[Drawing 12]

ATOM	109	O	LYS A	20	40.182	65.870	82.341	1.00	29.05
ATOM	110	CB	LYS A	20	43.239	65.608	83.187	1.00	30.61
ATOM	111	CG	LYS A	20	44.400	64.791	83.648	1.00	32.90
ATOM	112	CD	LYS A	20	45.633	65.326	82.963	1.00	39.72
ATOM	113	CE	LYS A	20	46.698	64.259	83.113	1.00	50.27
ATOM	114	NZ	LYS A	20	46.148	62.977	82.610	1.00	62.00
ATOM	115	N	ASN A	21	41.050	67.184	83.943	1.00	24.09
ATOM	116	CA	ASN A	21	40.154	68.246	83.530	1.00	23.98
ATOM	117	C	ASN A	21	40.177	68.539	82.032	1.00	25.08
ATOM	118	O	ASN A	21	39.134	68.722	81.427	1.00	25.36
ATOM	119	CB	ASN A	21	40.310	69.512	84.371	1.00	23.81
ATOM	120	CG	ASN A	21	39.601	69.311	85.697	1.00	26.97
ATOM	121	OD1	ASN A	21	38.392	69.175	85.836	1.00	26.36
ATOM	122	ND2	ASN A	21	40.403	69.303	86.744	1.00	32.00
ATOM	123	N	SER A	22	41.378	68.486	81.450	1.00	23.72
ATOM	124	CA	SER A	22	41.592	68.804	80.008	1.00	25.53
ATOM	125	C	SER A	22	40.992	67.752	79.068	1.00	25.77
ATOM	126	O	SER A	22	40.524	68.007	77.966	1.00	27.65
ATOM	127	CB	SER A	22	43.079	68.868	79.699	1.00	23.34
ATOM	128	OG	SER A	22	43.719	67.716	80.303	1.00	33.30
ATOM	129	N	GLU A	23	40.957	66.529	79.624	1.00	22.35
ATOM	130	CA	GLU A	23	40.320	65.466	78.899	1.00	21.87
ATOM	131	C	GLU A	23	38.811	65.375	78.974	1.00	23.18
ATOM	132	O	GLU A	23	38.197	64.451	78.471	1.00	25.83
ATOM	133	CB	GLU A	23	40.923	64.165	79.337	1.00	22.13
ATOM	134	CG	GLU A	23	42.451	64.215	79.214	1.00	26.78
ATOM	135	CD	GLU A	23	43.021	62.908	79.718	1.00	30.40
ATOM	136	OE1	GLU A	23	42.946	62.648	80.900	1.00	31.10
ATOM	137	OE2	GLU A	23	43.544	62.118	78.957	1.00	32.35
ATOM	138	N	ALA A	24	38.196	66.359	79.610	1.00	21.49
ATOM	139	CA	ALA A	24	36.751	66.165	79.738	1.00	22.48
ATOM	140	C	ALA A	24	35.973	66.420	78.438	1.00	22.81
ATOM	141	O	ALA A	24	36.325	67.333	77.704	1.00	23.36
ATOM	142	CB	ALA A	24	36.188	67.183	80.734	1.00	21.43
ATOM	143	N	ILE A	25	34.859	65.694	78.228	1.00	23.46
ATOM	144	CA	ILE A	25	33.845	66.149	77.243	1.00	23.60
ATOM	145	C	ILE A	25	33.312	67.535	77.530	1.00	24.71
ATOM	146	O	ILE A	25	32.788	67.809	78.603	1.00	25.03
ATOM	147	CB	ILE A	25	32.684	65.160	77.096	1.00	20.26
ATOM	148	CG1	ILE A	25	33.237	63.749	76.838	1.00	23.14
ATOM	149	CG2	ILE A	25	31.739	65.555	75.954	1.00	21.26
ATOM	150	CD1	ILE A	25	34.298	63.551	75.722	1.00	16.94
ATOM	151	N	ASN A	26	33.485	68.431	76.562	1.00	22.50
ATOM	152	CA	ASN A	26	32.797	69.706	76.751	1.00	22.04
ATOM	153	C	ASN A	26	31.295	69.680	76.533	1.00	22.52
ATOM	154	O	ASN A	26	30.731	70.042	75.509	1.00	22.34
ATOM	155	CB	ASN A	26	33.474	70.744	75.900	1.00	20.15
ATOM	156	CG	ASN A	26	32.982	72.133	76.217	1.00	24.94
ATOM	157	OD1	ASN A	26	31.923	72.459	76.732	1.00	29.46
ATOM	158	ND2	ASN A	26	33.827	73.032	75.809	1.00	25.76
ATOM	159	N	SER A	27	30.627	69.289	77.622	1.00	19.77
ATOM	160	CA	SER A	27	29.166	69.168	77.549	1.00	18.88
ATOM	161	C	SER A	27	28.412	70.423	77.177	1.00	18.74
ATOM	162	O	SER A	27	27.390	70.393	76.517	1.00	21.73

[Drawing 13]

ATOM	163	CB	SER A	27	28.606	68.619	78.870	1.00	19.35
ATOM	164	OG	SER A	27	28.967	69.518	79.940	1.00	19.36
ATOM	165	N	LEU A	28	28.961	71.564	77.588	1.00	18.08
ATOM	166	CA	LEU A	28	28.271	72.815	77.262	1.00	20.15
ATOM	167	C	LEU A	28	28.283	73.062	75.761	1.00	23.12
ATOM	168	O	LEU A	28	27.303	73.485	75.165	1.00	22.25
ATOM	169	CB	LEU A	28	28.990	74.042	77.798	1.00	17.00
ATOM	170	CG	LEU A	28	28.159	75.188	78.376	1.00	18.01
ATOM	171	CD1	LEU A	28	26.847	75.547	77.733	1.00	14.28
ATOM	172	CD2	LEU A	28	29.053	76.394	78.592	1.00	16.45
ATOM	173	N	ALA A	29	29.478	72.767	75.193	1.00	23.87
ATOM	174	CA	ALA A	29	29.598	72.827	73.707	1.00	22.62
ATOM	175	C	ALA A	29	28.773	71.847	72.837	1.00	20.86
ATOM	176	O	ALA A	29	28.192	72.239	71.830	1.00	25.89
ATOM	177	CB	ALA A	29	31.065	72.692	73.326	1.00	20.24
ATOM	178	N	LEU A	30	28.733	70.580	73.267	1.00	15.78
ATOM	179	CA	LEU A	30	28.079	69.497	72.519	1.00	18.05
ATOM	180	C	LEU A	30	26.557	69.416	72.559	1.00	22.38
ATOM	181	O	LEU A	30	25.845	69.251	71.566	1.00	23.63
ATOM	182	CB	LEU A	30	28.732	68.194	72.977	1.00	16.47
ATOM	183	CG	LEU A	30	28.234	66.887	72.360	1.00	17.59
ATOM	184	CD1	LEU A	30	28.812	65.706	73.120	1.00	12.95
ATOM	185	CD2	LEU A	30	28.456	66.775	70.850	1.00	13.89
ATOM	186	N	LEU A	31	26.075	69.533	73.812	1.00	22.39
ATOM	187	CA	LEU A	31	24.633	69.430	74.049	1.00	18.84
ATOM	188	C	LEU A	31	23.817	70.624	73.538	1.00	16.30
ATOM	189	O	LEU A	31	24.260	71.763	73.576	1.00	19.93
ATOM	190	CB	LEU A	31	24.381	69.199	75.556	1.00	16.94
ATOM	191	CG	LEU A	31	24.923	67.873	76.095	1.00	17.95
ATOM	192	CD1	LEU A	31	24.177	66.669	75.553	1.00	11.60
ATOM	193	CD2	LEU A	31	24.823	67.878	77.628	1.00	18.77
ATOM	194	N	PRO A	32	22.581	70.333	73.105	1.00	14.80
ATOM	195	CA	PRO A	32	21.589	71.404	72.910	1.00	18.31
ATOM	196	C	PRO A	32	21.228	72.028	74.278	1.00	22.24
ATOM	197	O	PRO A	32	21.453	71.442	75.327	1.00	22.27
ATOM	198	CB	PRO A	32	20.402	70.621	72.348	1.00	15.94
ATOM	199	CG	PRO A	32	20.545	69.184	72.847	1.00	16.93
ATOM	200	CD	PRO A	32	22.038	68.972	72.954	1.00	15.56
ATOM	201	N	PRO A	33	20.657	73.249	74.287	1.00	23.41
ATOM	202	CA	PRO A	33	20.190	73.780	75.586	1.00	20.34
ATOM	203	C	PRO A	33	19.059	72.945	76.084	1.00	19.93
ATOM	204	O	PRO A	33	18.409	72.292	75.285	1.00	18.67
ATOM	205	CB	PRO A	33	19.659	75.158	75.224	1.00	18.52
ATOM	206	CG	PRO A	33	20.267	75.499	73.877	1.00	21.71
ATOM	207	CD	PRO A	33	20.406	74.146	73.177	1.00	21.12
ATOM	208	N	PRO A	34	18.785	72.950	77.411	1.00	19.36
ATOM	209	CA	PRO A	34	17.645	72.138	77.863	1.00	13.70
ATOM	210	C	PRO A	34	16.348	72.759	77.351	1.00	11.77
ATOM	211	O	PRO A	34	16.280	73.937	77.090	1.00	14.58
ATOM	212	CB	PRO A	34	17.760	72.358	79.389	1.00	13.66
ATOM	213	CG	PRO A	34	18.471	73.698	79.571	1.00	14.81
ATOM	214	CD	PRO A	34	19.499	73.679	78.464	1.00	16.49
ATOM	215	N	PRO A	35	15.257	72.007	77.284	1.00	12.52
ATOM	216	CA	PRO A	35	14.011	72.710	76.973	1.00	13.71

[Drawing 14]

ATOM	217	C	PRO	A	35	13.665	73.842	77.945	1.00	20.26
ATOM	218	O	PRO	A	35	13.728	73.715	79.159	1.00	20.52
ATOM	219	CB	PRO	A	35	12.997	71.579	76.991	1.00	11.74
ATOM	220	CG	PRO	A	35	13.723	70.243	77.051	1.00	12.04
ATOM	221	CD	PRO	A	35	15.140	70.581	77.482	1.00	11.57
ATOM	222	N	ALA	A	36	13.311	74.962	77.356	1.00	19.25
ATOM	223	CA	ALA	A	36	12.919	76.136	78.122	1.00	18.78
ATOM	224	C	ALA	A	36	11.457	76.120	78.497	1.00	18.25
ATOM	225	O	ALA	A	36	10.582	75.579	77.847	1.00	18.88
ATOM	226	CB	ALA	A	36	13.152	77.414	77.304	1.00	17.95
ATOM	227	N	VAL	A	37	11.182	76.753	79.609	1.00	18.03
ATOM	228	CA	VAL	A	37	9.803	77.005	79.965	1.00	16.78
ATOM	229	C	VAL	A	37	9.135	77.993	78.998	1.00	17.18
ATOM	230	O	VAL	A	37	9.640	79.048	78.650	1.00	19.89
ATOM	231	CB	VAL	A	37	9.740	77.500	81.436	1.00	18.33
ATOM	232	CG1	VAL	A	37	10.381	76.501	82.418	1.00	13.83
ATOM	233	CG2	VAL	A	37	8.300	77.825	81.832	1.00	14.21
ATOM	234	N	GLY	A	38	7.952	77.616	78.561	1.00	18.34
ATOM	235	CA	GLY	A	38	7.422	78.249	77.343	1.00	22.06
ATOM	236	C	GLY	A	38	7.538	77.398	76.043	1.00	21.25
ATOM	237	O	GLY	A	38	6.851	77.623	75.068	1.00	22.09
ATOM	238	N	SER	A	39	8.422	76.401	76.060	1.00	21.73
ATOM	239	CA	SER	A	39	8.520	75.487	74.905	1.00	20.30
ATOM	240	C	SER	A	39	7.604	74.277	74.964	1.00	21.10
ATOM	241	O	SER	A	39	7.217	73.736	76.002	1.00	19.55
ATOM	242	CB	SER	A	39	9.946	74.998	74.748	1.00	15.45
ATOM	243	OG	SER	A	39	10.197	73.967	75.704	1.00	15.38
ATOM	244	N	ILE	A	40	7.287	73.796	73.772	1.00	17.17
ATOM	245	CA	ILE	A	40	6.618	72.485	73.702	1.00	14.71
ATOM	246	C	ILE	A	40	7.475	71.311	74.225	1.00	10.81
ATOM	247	O	ILE	A	40	6.998	70.315	74.782	1.00	15.23
ATOM	248	CB	ILE	A	40	6.102	72.235	72.219	1.00	15.78
ATOM	249	CG1	ILE	A	40	5.162	73.368	71.791	1.00	15.41
ATOM	250	CG2	ILE	A	40	5.406	70.863	72.091	1.00	14.54
ATOM	251	CD1	ILE	A	40	4.812	73.332	70.307	1.00	18.26
ATOM	252	N	ALA	A	41	8.790	71.443	74.040	1.00	10.69
ATOM	253	CA	ALA	A	41	9.633	70.373	74.530	1.00	13.79
ATOM	254	C	ALA	A	41	9.566	70.300	76.091	1.00	15.36
ATOM	255	O	ALA	A	41	9.369	69.245	76.683	1.00	20.02
ATOM	256	CB	ALA	A	41	11.046	70.610	74.065	1.00	11.61
ATOM	257	N	PHE	A	42	9.547	71.495	76.702	1.00	16.94
ATOM	258	CA	PHE	A	42	9.200	71.480	78.151	1.00	15.75
ATOM	259	C	PHE	A	42	7.818	70.970	78.533	1.00	16.07
ATOM	260	O	PHE	A	42	7.652	70.182	79.448	1.00	19.72
ATOM	261	CB	PHE	A	42	9.513	72.819	78.819	1.00	17.93
ATOM	262	CG	PHE	A	42	9.380	72.700	80.338	1.00	20.96
ATOM	263	CD1	PHE	A	42	10.297	71.904	81.056	1.00	19.46
ATOM	264	CD2	PHE	A	42	8.324	73.370	80.997	1.00	20.99
ATOM	265	CE1	PHE	A	42	10.148	71.763	82.450	1.00	17.30
ATOM	266	CE2	PHE	A	42	8.190	73.248	82.402	1.00	19.79
ATOM	267	CZ	PHE	A	42	9.111	72.443	83.100	1.00	13.36
ATOM	268	N	LEU	A	43	6.790	71.375	77.765	1.00	19.00
ATOM	269	CA	LEU	A	43	5.507	70.643	77.917	1.00	19.22
ATOM	270	C	LEU	A	43	5.573	69.103	77.945	1.00	19.39

[Drawing 15]

ATOM	271	O	LEU	A	43	4.957	68.410	78.749	1.00	17.69
ATOM	272	CB	LEU	A	43	4.472	71.003	76.826	1.00	21.60
ATOM	273	CG	LEU	A	43	3.213	71.850	77.034	1.00	24.67
ATOM	274	CD1	LEU	A	43	2.597	71.800	78.433	1.00	17.68
ATOM	275	CD2	LEU	A	43	2.172	71.549	75.953	1.00	21.72
ATOM	276	N	ASN	A	44	6.392	68.588	77.023	1.00	19.47
ATOM	277	CA	ASN	A	44	6.653	67.176	77.076	1.00	19.82
ATOM	278	C	ASN	A	44	7.419	66.619	78.312	1.00	17.44
ATOM	279	O	ASN	A	44	7.018	65.604	78.855	1.00	15.52
ATOM	280	CB	ASN	A	44	7.259	66.847	75.747	1.00	19.07
ATOM	281	CG	ASN	A	44	7.491	65.366	75.643	1.00	22.97
ATOM	282	OD1	ASN	A	44	8.605	64.906	75.468	1.00	30.35
ATOM	283	ND2	ASN	A	44	6.444	64.588	75.862	1.00	22.13
ATOM	284	N	ASP	A	45	8.482	67.324	78.726	1.00	19.71
ATOM	285	CA	ASP	A	45	9.175	67.050	80.020	1.00	19.87
ATOM	286	C	ASP	A	45	8.192	66.977	81.213	1.00	19.30
ATOM	287	O	ASP	A	45	8.103	66.009	81.956	1.00	21.00
ATOM	288	CB	ASP	A	45	10.225	68.119	80.273	1.00	13.57
ATOM	289	CG	ASP	A	45	11.563	67.769	79.706	1.00	12.64
ATOM	290	OD1	ASP	A	45	12.408	68.656	79.625	1.00	15.68
ATOM	291	OD2	ASP	A	45	11.823	66.611	79.414	1.00	14.57
ATOM	292	N	GLN	A	46	7.347	68.007	81.299	1.00	19.62
ATOM	293	CA	GLN	A	46	6.199	67.904	82.220	1.00	19.44
ATOM	294	C	GLN	A	46	5.259	66.702	82.166	1.00	22.23
ATOM	295	O	GLN	A	46	4.960	66.057	83.175	1.00	21.67
ATOM	296	CB	GLN	A	46	5.353	69.153	82.218	1.00	16.35
ATOM	297	CG	GLN	A	46	6.282	70.333	82.395	1.00	18.35
ATOM	298	CD	GLN	A	46	5.398	71.519	82.591	1.00	26.07
ATOM	299	OE1	GLN	A	46	5.334	72.143	83.629	1.00	31.83
ATOM	300	NE2	GLN	A	46	4.622	71.823	81.591	1.00	22.82
ATOM	301	N	ALA	A	47	4.838	66.364	80.935	1.00	19.12
ATOM	302	CA	ALA	A	47	3.979	65.187	80.813	1.00	17.83
ATOM	303	C	ALA	A	47	4.661	63.871	81.172	1.00	15.90
ATOM	304	O	ALA	A	47	4.065	62.940	81.701	1.00	18.55
ATOM	305	CB	ALA	A	47	3.441	65.066	79.367	1.00	17.11
ATOM	306	N	MET	A	48	5.970	63.818	80.841	1.00	18.16
ATOM	307	CA	MET	A	48	6.799	62.644	81.235	1.00	19.52
ATOM	308	C	MET	A	48	7.012	62.460	82.765	1.00	21.38
ATOM	309	O	MET	A	48	6.996	61.358	83.316	1.00	20.83
ATOM	310	CB	MET	A	48	8.173	62.667	80.539	1.00	21.42
ATOM	311	CG	MET	A	48	8.150	62.603	78.984	1.00	29.81
ATOM	312	SD	MET	A	48	7.330	61.126	78.308	1.00	36.20
ATOM	313	CE	MET	A	48	5.582	61.633	78.280	1.00	33.60
ATOM	314	N	TYR	A	49	7.139	63.655	83.414	1.00	21.32
ATOM	315	CA	TYR	A	49	7.066	63.807	84.885	1.00	21.30
ATOM	316	C	TYR	A	49	5.773	63.244	85.515	1.00	22.58
ATOM	317	O	TYR	A	49	5.797	62.383	86.390	1.00	24.04
ATOM	318	CB	TYR	A	49	7.304	65.282	85.217	1.00	20.61
ATOM	319	CG	TYR	A	49	7.034	65.494	86.692	1.00	23.57
ATOM	320	CD1	TYR	A	49	5.755	65.931	87.109	1.00	23.57
ATOM	321	CD2	TYR	A	49	8.080	65.194	87.574	1.00	21.83
ATOM	322	CE1	TYR	A	49	5.524	66.097	88.481	1.00	26.09
ATOM	323	CE2	TYR	A	49	7.844	65.349	88.943	1.00	23.18
ATOM	324	CZ	TYR	A	49	6.591	65.842	89.377	1.00	26.31

[Drawing 16]

ATOM	325	OH	TYR	A	49	6.444	66.124	90.726	1.00	29.46
ATOM	326	N	GLU	A	50	4.639	63.731	84.994	1.00	22.09
ATOM	327	CA	GLU	A	50	3.336	63.234	85.472	1.00	21.48
ATOM	328	C	GLU	A	50	3.052	61.776	85.230	1.00	23.20
ATOM	329	O	GLU	A	50	2.548	61.050	86.081	1.00	24.23
ATOM	330	CB	GLU	A	50	2.190	64.023	84.862	1.00	21.88
ATOM	331	CG	GLU	A	50	2.304	65.537	84.986	1.00	21.13
ATOM	332	CD	GLU	A	50	2.054	65.976	86.417	1.00	25.41
ATOM	333	OE1	GLU	A	50	1.887	65.138	87.287	1.00	24.65
ATOM	334	OE2	GLU	A	50	2.004	67.162	86.679	1.00	25.05
ATOM	335	N	GLN	A	51	3.479	61.343	84.032	1.00	23.02
ATOM	336	CA	GLN	A	51	3.427	59.907	83.812	1.00	24.72
ATOM	337	C	GLN	A	51	4.275	59.006	84.728	1.00	26.23
ATOM	338	O	GLN	A	51	3.804	57.996	85.253	1.00	25.10
ATOM	339	CB	GLN	A	51	3.680	59.545	82.355	1.00	24.41
ATOM	340	CG	GLN	A	51	3.461	58.028	82.141	1.00	38.05
ATOM	341	CD	GLN	A	51	2.115	57.435	82.657	1.00	53.15
ATOM	342	OE1	GLN	A	51	1.093	58.076	82.867	1.00	61.03
ATOM	343	NE2	GLN	A	51	2.098	56.123	82.834	1.00	55.24
ATOM	344	N	GLY	A	52	5.556	59.414	84.922	1.00	26.76
ATOM	345	CA	GLY	A	52	6.400	58.689	85.876	1.00	26.91
ATOM	346	C	GLY	A	52	5.793	58.681	87.286	1.00	25.60
ATOM	347	O	GLY	A	52	5.666	57.699	87.997	1.00	24.37
ATOM	348	N	ARG	A	53	5.321	59.874	87.621	1.00	28.09
ATOM	349	CA	ARG	A	53	4.527	60.032	88.834	1.00	29.75
ATOM	350	C	ARG	A	53	3.384	59.049	89.067	1.00	32.01
ATOM	351	O	ARG	A	53	3.284	58.437	90.115	1.00	34.69
ATOM	352	CB	ARG	A	53	4.128	61.494	88.965	1.00	30.41
ATOM	353	CG	ARG	A	53	3.857	61.919	90.389	1.00	29.15
ATOM	354	CD	ARG	A	53	3.519	63.393	90.461	1.00	29.38
ATOM	355	NE	ARG	A	53	2.385	63.740	89.609	1.00	31.35
ATOM	356	CZ	ARG	A	53	1.088	63.593	89.886	1.00	32.29
ATOM	357	NH1	ARG	A	53	0.187	64.144	89.125	1.00	32.06
ATOM	358	NH2	ARG	A	53	0.661	62.938	90.931	1.00	32.66
ATOM	359	N	LEU	A	54	2.575	58.839	88.033	1.00	32.47
ATOM	360	CA	LEU	A	54	1.588	57.735	88.076	1.00	31.67
ATOM	361	C	LEU	A	54	2.114	56.273	88.119	1.00	33.30
ATOM	362	O	LEU	A	54	1.452	55.329	88.568	1.00	35.90
ATOM	363	CB	LEU	A	54	0.603	57.880	86.901	1.00	33.52
ATOM	364	CG	LEU	A	54	-0.599	58.822	87.055	1.00	32.85
ATOM	365	CD1	LEU	A	54	-1.298	59.020	85.709	1.00	30.53
ATOM	366	CD2	LEU	A	54	-0.286	60.130	87.777	1.00	36.56
ATOM	367	N	LEU	A	55	3.374	56.117	87.657	1.00	31.95
ATOM	368	CA	LEU	A	55	4.016	54.784	87.735	1.00	32.70
ATOM	369	C	LEU	A	55	4.577	54.392	89.091	1.00	33.98
ATOM	370	O	LEU	A	55	4.842	53.224	89.386	1.00	32.73
ATOM	371	CB	LEU	A	55	5.194	54.646	86.790	1.00	31.04
ATOM	372	CG	LEU	A	55	4.832	54.514	85.343	1.00	28.60
ATOM	373	CD1	LEU	A	55	3.960	53.287	85.101	1.00	27.88
ATOM	374	CD2	LEU	A	55	6.118	54.471	84.539	1.00	28.33
ATOM	375	N	ARG	A	56	4.732	55.458	89.911	1.00	36.20
ATOM	376	CA	ARG	A	56	5.257	55.308	91.281	1.00	37.04
ATOM	377	C	ARG	A	56	4.616	54.240	92.164	1.00	40.28
ATOM	378	O	ARG	A	56	5.260	53.518	92.907	1.00	41.22

[Drawing 17]

ATOM	379	CB	ARG	A	56	5.249	56.643	91.993	1.00	32.58
ATOM	380	CG	ARG	A	56	6.368	57.502	91.476	1.00	22.04
ATOM	381	CD	ARG	A	56	6.142	58.874	92.049	1.00	21.74
ATOM	382	NE	ARG	A	56	7.073	59.804	91.447	1.00	23.56
ATOM	383	CZ	ARG	A	56	7.062	61.074	91.750	1.00	25.56
ATOM	384	NH1	ARG	A	56	6.401	61.444	92.790	1.00	30.94
ATOM	385	NH2	ARG	A	56	7.688	61.979	91.035	1.00	22.33
ATOM	386	N	ASN	A	57	3.306	54.120	91.997	1.00	44.42
ATOM	387	CA	ASN	A	57	2.602	53.027	92.680	1.00	48.62
ATOM	388	C	ASN	A	57	2.786	51.585	92.169	1.00	47.46
ATOM	389	O	ASN	A	57	2.316	50.630	92.759	1.00	51.15
ATOM	390	CB	ASN	A	57	1.124	53.435	92.726	1.00	59.30
ATOM	391	CG	ASN	A	57	0.389	53.137	94.049	1.00	68.98
ATOM	392	OD1	ASN	A	57	-0.829	53.335	94.164	1.00	75.09
ATOM	393	ND2	ASN	A	57	1.140	52.692	95.058	1.00	71.68
ATOM	394	N	THR	A	58	3.461	51.442	91.036	1.00	42.68
ATOM	395	CA	THR	A	58	3.555	50.086	90.475	1.00	36.64
ATOM	396	C	THR	A	58	4.821	49.318	90.871	1.00	33.64
ATOM	397	O	THR	A	58	5.721	49.876	91.477	1.00	31.69
ATOM	398	CB	THR	A	58	3.492	50.189	88.948	1.00	36.81
ATOM	399	OG1	THR	A	58	4.774	50.576	88.447	1.00	37.64
ATOM	400	CG2	THR	A	58	2.432	51.203	88.507	1.00	35.36
ATOM	401	N	GLU	A	59	4.937	48.068	90.409	1.00	33.08
ATOM	402	CA	GLU	A	59	6.238	47.410	90.581	1.00	34.80
ATOM	403	C	GLU	A	59	7.487	48.104	89.944	1.00	33.45
ATOM	404	O	GLU	A	59	8.607	48.153	90.463	1.00	34.28
ATOM	405	CB	GLU	A	59	6.067	45.933	90.191	1.00	43.43
ATOM	406	CG	GLU	A	59	7.242	45.007	90.614	1.00	59.74
ATOM	407	CD	GLU	A	59	7.519	44.933	92.159	1.00	69.61
ATOM	408	OE1	GLU	A	59	6.582	45.064	92.960	1.00	74.78
ATOM	409	OE2	GLU	A	59	8.686	44.751	92.589	1.00	74.97
ATOM	410	N	ARG	A	60	7.229	48.734	88.768	1.00	27.61
ATOM	411	CA	ARG	A	60	8.251	49.599	88.158	1.00	25.02
ATOM	412	C	ARG	A	60	8.614	50.851	88.958	1.00	22.94
ATOM	413	O	ARG	A	60	9.772	51.257	89.002	1.00	24.63
ATOM	414	CB	ARG	A	60	7.874	49.966	86.690	1.00	26.16
ATOM	415	CG	ARG	A	60	8.877	50.860	85.900	1.00	24.47
ATOM	416	CD	ARG	A	60	10.268	50.249	85.758	1.00	23.96
ATOM	417	NE	ARG	A	60	11.285	51.161	85.217	1.00	25.64
ATOM	418	CZ	ARG	A	60	12.214	51.778	85.945	1.00	24.77
ATOM	419	NH1	ARG	A	60	12.159	51.805	87.261	1.00	24.78
ATOM	420	NH2	ARG	A	60	13.227	52.294	85.325	1.00	19.79
ATOM	421	N	GLY	A	61	7.562	51.411	89.587	1.00	21.94
ATOM	422	CA	GLY	A	61	7.623	52.443	90.620	1.00	22.33
ATOM	423	C	GLY	A	61	8.468	52.051	91.824	1.00	24.44
ATOM	424	O	GLY	A	61	9.350	52.773	92.253	1.00	25.22
ATOM	425	N	LYS	A	62	8.248	50.821	92.307	1.00	26.95
ATOM	426	CA	LYS	A	62	9.102	50.251	93.350	1.00	26.24
ATOM	427	C	LYS	A	62	10.590	50.158	93.045	1.00	24.89
ATOM	428	O	LYS	A	62	11.443	50.668	93.756	1.00	23.23
ATOM	429	CB	LYS	A	62	8.519	48.900	93.723	1.00	29.90
ATOM	430	CG	LYS	A	62	9.379	48.296	94.835	1.00	38.76
ATOM	431	CD	LYS	A	62	8.847	46.904	95.222	1.00	47.47
ATOM	432	CE	LYS	A	62	9.944	45.971	95.773	1.00	53.72

[Drawing 18]



ATOM	433	NZ	LYS	A	62	10.167	44.857	94.832	1.00	60.22
ATOM	434	N	LEU	A	63	10.866	49.560	91.882	1.00	24.67
ATOM	435	CA	LEU	A	63	12.239	49.634	91.346	1.00	23.65
ATOM	436	C	LEU	A	63	12.805	51.043	91.186	1.00	22.74
ATOM	437	O	LEU	A	63	13.927	51.359	91.517	1.00	25.19
ATOM	438	CB	LEU	A	63	12.232	48.973	89.981	1.00	27.11
ATOM	439	CG	LEU	A	63	13.477	48.298	89.403	1.00	31.83
ATOM	440	CD1	LEU	A	63	14.808	48.658	90.077	1.00	33.84
ATOM	441	CD2	LEU	A	63	13.440	48.410	87.874	1.00	26.95
ATOM	442	N	ALA	A	64	11.979	51.940	90.642	1.00	21.62
ATOM	443	CA	ALA	A	64	12.492	53.308	90.539	1.00	20.51
ATOM	444	C	ALA	A	64	12.862	53.971	91.863	1.00	21.79
ATOM	445	O	ALA	A	64	13.890	54.636	91.984	1.00	21.21
ATOM	446	CB	ALA	A	64	11.456	54.196	89.862	1.00	19.01
ATOM	447	N	ALA	A	65	11.984	53.747	92.870	1.00	23.25
ATOM	448	CA	ALA	A	65	12.374	54.212	94.235	1.00	24.88
ATOM	449	C	ALA	A	65	13.684	53.619	94.784	1.00	22.62
ATOM	450	O	ALA	A	65	14.551	54.328	95.268	1.00	22.95
ATOM	451	CB	ALA	A	65	11.249	54.013	95.265	1.00	25.38
ATOM	452	N	GLU	A	66	13.848	52.295	94.572	1.00	23.38
ATOM	453	CA	GLU	A	66	15.116	51.632	94.878	1.00	23.41
ATOM	454	C	GLU	A	66	16.332	52.188	94.152	1.00	26.06
ATOM	455	O	GLU	A	66	17.321	52.604	94.744	1.00	25.12
ATOM	456	CB	GLU	A	66	14.968	50.136	94.665	1.00	25.85
ATOM	457	CG	GLU	A	66	13.818	49.616	95.533	1.00	31.94
ATOM	458	CD	GLU	A	66	13.546	48.142	95.293	1.00	37.59
ATOM	459	OE1	GLU	A	66	13.147	47.430	96.220	1.00	40.33
ATOM	460	OE2	GLU	A	66	13.721	47.673	94.176	1.00	40.79
ATOM	461	N	ASP	A	67	16.204	52.276	92.817	1.00	24.01
ATOM	462	CA	ASP	A	67	17.222	52.928	91.986	1.00	19.72
ATOM	463	C	ASP	A	67	17.549	54.333	92.402	1.00	16.72
ATOM	464	O	ASP	A	67	18.694	54.767	92.414	1.00	18.91
ATOM	465	CB	ASP	A	67	16.787	52.944	90.495	1.00	21.68
ATOM	466	CG	ASP	A	67	16.824	51.580	89.801	1.00	25.22
ATOM	467	OD1	ASP	A	67	17.340	50.629	90.370	1.00	23.32
ATOM	468	OD2	ASP	A	67	16.349	51.434	88.666	1.00	26.83
ATOM	469	N	ALA	A	68	16.485	55.059	92.773	1.00	16.48
ATOM	470	CA	ALA	A	68	16.685	56.425	93.250	1.00	19.28
ATOM	471	C	ALA	A	68	17.489	56.510	94.569	1.00	20.86
ATOM	472	O	ALA	A	68	18.165	57.494	94.837	1.00	22.07
ATOM	473	CB	ALA	A	68	15.330	57.134	93.419	1.00	19.81
ATOM	474	N	ASN	A	69	17.472	55.371	95.299	1.00	23.11
ATOM	475	CA	ASN	A	69	18.330	55.262	96.514	1.00	27.41
ATOM	476	C	ASN	A	69	19.816	55.042	96.273	1.00	29.49
ATOM	477	O	ASN	A	69	20.646	55.304	97.140	1.00	28.64
ATOM	478	CB	ASN	A	69	17.933	54.145	97.466	1.00	24.19
ATOM	479	CG	ASN	A	69	16.632	54.425	98.142	1.00	25.79
ATOM	480	OD1	ASN	A	69	16.298	55.549	98.445	1.00	26.84
ATOM	481	ND2	ASN	A	69	15.894	53.359	98.410	1.00	30.16
ATOM	482	N	LEU	A	70	20.104	54.574	95.034	1.00	25.30
ATOM	483	CA	LEU	A	70	21.514	54.442	94.627	1.00	23.20
ATOM	484	C	LEU	A	70	22.329	55.691	94.640	1.00	21.41
ATOM	485	O	LEU	A	70	22.013	56.696	94.028	1.00	23.50
ATOM	486	CB	LEU	A	70	21.672	53.890	93.225	1.00	22.19

[Drawing 19]

ATOM	487	CG	LEU	A	70	21.078	52.512	93.095	1.00	22.16
ATOM	488	CD1	LEU	A	70	21.830	51.459	93.896	1.00	20.70
ATOM	489	CD2	LEU	A	70	21.016	52.154	91.624	1.00	23.47
ATOM	490	N	SER	A	71	23.450	55.563	95.304	1.00	21.73
ATOM	491	CA	SER	A	71	24.527	56.515	95.119	1.00	22.25
ATOM	492	C	SER	A	71	25.355	56.171	93.888	1.00	20.52
ATOM	493	O	SER	A	71	25.269	55.081	93.357	1.00	23.70
ATOM	494	CB	SER	A	71	25.453	56.521	96.349	1.00	22.74
ATOM	495	OG	SER	A	71	26.232	55.303	96.432	1.00	28.68
ATOM	496	N	SER	A	72	26.220	57.079	93.445	1.00	20.02
ATOM	497	CA	SER	A	72	27.096	56.747	92.294	1.00	20.88
ATOM	498	C	SER	A	72	27.860	55.479	92.410	1.00	22.52
ATOM	499	O	SER	A	72	27.979	54.663	91.518	1.00	21.65
ATOM	500	CB	SER	A	72	28.113	57.834	92.083	1.00	19.05
ATOM	501	OG	SER	A	72	27.352	58.966	91.735	1.00	22.00
ATOM	502	N	GLY	A	73	28.336	55.318	93.640	1.00	20.71
ATOM	503	CA	GLY	A	73	28.979	54.068	94.006	1.00	16.81
ATOM	504	C	GLY	A	73	28.146	52.783	93.939	1.00	15.97
ATOM	505	O	GLY	A	73	28.697	51.705	93.753	1.00	20.02
ATOM	506	N	GLY	A	74	26.818	52.915	94.046	1.00	16.07
ATOM	507	CA	GLY	A	74	26.090	51.649	93.967	1.00	18.17
ATOM	508	C	GLY	A	74	25.671	51.260	92.526	1.00	21.98
ATOM	509	O	GLY	A	74	25.202	50.164	92.238	1.00	21.28
ATOM	510	N	VAL	A	75	25.887	52.210	91.567	1.00	22.48
ATOM	511	CA	VAL	A	75	25.521	51.777	90.174	1.00	22.71
ATOM	512	C	VAL	A	75	26.174	50.493	89.628	1.00	18.50
ATOM	513	O	VAL	A	75	25.497	49.573	89.210	1.00	20.32
ATOM	514	CB	VAL	A	75	25.820	52.946	89.218	1.00	23.52
ATOM	515	CG1	VAL	A	75	25.719	52.707	87.712	1.00	21.49
ATOM	516	CG2	VAL	A	75	25.153	54.265	89.560	1.00	17.54
ATOM	517	N	ALA	A	76	27.517	50.394	89.738	1.00	21.05
ATOM	518	CA	ALA	A	76	28.149	49.125	89.372	1.00	20.51
ATOM	519	C	ALA	A	76	27.414	47.875	89.826	1.00	24.64
ATOM	520	O	ALA	A	76	27.033	47.028	89.015	1.00	24.90
ATOM	521	CB	ALA	A	76	29.612	49.071	89.810	1.00	19.14
ATOM	522	N	ASN	A	77	27.131	47.820	91.145	1.00	20.97
ATOM	523	CA	ASN	A	77	26.463	46.601	91.622	1.00	17.62
ATOM	524	C	ASN	A	77	25.019	46.464	91.205	1.00	16.57
ATOM	525	O	ASN	A	77	24.536	45.350	91.024	1.00	19.24
ATOM	526	CB	ASN	A	77	26.615	46.509	93.137	1.00	23.52
ATOM	527	CG	ASN	A	77	25.817	45.362	93.677	1.00	21.57
ATOM	528	OD1	ASN	A	77	24.672	45.508	94.079	1.00	26.66
ATOM	529	ND2	ASN	A	77	26.435	44.202	93.627	1.00	24.64
ATOM	530	N	ALA	A	78	24.377	47.638	91.017	1.00	17.23
ATOM	531	CA	ALA	A	78	23.060	47.710	90.339	1.00	18.62
ATOM	532	C	ALA	A	78	22.874	47.025	88.941	1.00	19.92
ATOM	533	O	ALA	A	78	21.767	46.705	88.517	1.00	21.04
ATOM	534	CB	ALA	A	78	22.636	49.160	90.208	1.00	13.62
ATOM	535	N	PHE	A	79	24.025	46.748	88.292	1.00	19.22
ATOM	536	CA	PHE	A	79	24.019	45.921	87.070	1.00	20.71
ATOM	537	C	PHE	A	79	24.117	44.420	87.238	1.00	23.30
ATOM	538	O	PHE	A	79	24.161	43.662	86.273	1.00	23.64
ATOM	539	CB	PHE	A	79	25.116	46.352	86.082	1.00	18.00
ATOM	540	CG	PHE	A	79	24.821	47.683	85.382	1.00	19.59

[Drawing 20]

ATOM	541	CD1	PHE	A	79	25.181	48.903	85.984	1.00	17.05
ATOM	542	CD2	PHE	A	79	24.214	47.687	84.104	1.00	18.56
ATOM	543	CE1	PHE	A	79	25.026	50.119	85.298	1.00	19.06
ATOM	544	CE2	PHE	A	79	24.040	48.906	83.419	1.00	15.97
ATOM	545	CZ	PHE	A	79	24.500	50.104	83.989	1.00	17.87
ATOM	546	N	SER	A	80	24.150	43.947	88.488	1.00	19.74
ATOM	547	CA	SER	A	80	24.500	42.511	88.632	1.00	17.29
ATOM	548	C	SER	A	80	23.601	41.501	87.944	1.00	18.57
ATOM	549	O	SER	A	80	23.977	40.494	87.339	1.00	22.38
ATOM	550	CB	SER	A	80	24.608	42.106	90.125	1.00	15.17
ATOM	551	OG	SER	A	80	25.646	42.920	90.700	1.00	17.32
ATOM	552	N	GLY	A	81	22.309	41.852	88.041	1.00	19.68
ATOM	553	CA	GLY	A	81	21.271	41.005	87.413	1.00	22.50
ATOM	554	C	GLY	A	81	21.293	40.977	85.855	1.00	24.85
ATOM	555	O	GLY	A	81	21.318	39.939	85.211	1.00	23.46
ATOM	556	N	ALA	A	82	21.380	42.197	85.279	1.00	24.60
ATOM	557	CA	ALA	A	82	21.686	42.339	83.855	1.00	24.50
ATOM	558	C	ALA	A	82	22.985	41.643	83.417	1.00	25.22
ATOM	559	O	ALA	A	82	23.000	40.873	82.468	1.00	23.42
ATOM	560	CB	ALA	A	82	21.649	43.819	83.470	1.00	20.35
ATOM	561	N	PHE	A	83	24.050	41.874	84.197	1.00	23.76
ATOM	562	CA	PHE	A	83	25.319	41.242	83.894	1.00	21.76
ATOM	563	C	PHE	A	83	25.325	39.726	83.974	1.00	22.85
ATOM	564	O	PHE	A	83	26.090	39.052	83.322	1.00	25.72
ATOM	565	CB	PHE	A	83	26.349	41.867	84.792	1.00	20.01
ATOM	566	CG	PHE	A	83	27.770	41.527	84.394	1.00	20.95
ATOM	567	CD1	PHE	A	83	28.486	40.587	85.152	1.00	16.94
ATOM	568	CD2	PHE	A	83	28.391	42.208	83.307	1.00	23.09
ATOM	569	CE1	PHE	A	83	29.841	40.355	84.843	1.00	18.79
ATOM	570	CE2	PHE	A	83	29.751	41.991	83.001	1.00	20.95
ATOM	571	CZ	PHE	A	83	30.474	41.069	83.795	1.00	21.43
ATOM	572	N	GLY	A	84	24.409	39.187	84.768	1.00	22.31
ATOM	573	CA	GLY	A	84	24.478	37.740	84.865	1.00	24.39
ATOM	574	C	GLY	A	84	25.199	37.163	86.093	1.00	29.49
ATOM	575	O	GLY	A	84	25.158	35.963	86.362	1.00	32.27
ATOM	576	N	SER	A	85	25.873	38.058	86.843	1.00	30.33
ATOM	577	CA	SER	A	85	26.685	37.625	88.001	1.00	28.46
ATOM	578	C	SER	A	85	27.047	38.788	88.936	1.00	29.06
ATOM	579	O	SER	A	85	26.915	39.945	88.556	1.00	29.00
ATOM	580	CB	SER	A	85	27.915	36.861	87.536	1.00	24.04
ATOM	581	OG	SER	A	85	28.903	37.746	87.028	1.00	28.11
ATOM	582	N	PRO	A	86	27.436	38.518	90.216	1.00	29.45
ATOM	583	CA	PRO	A	86	27.599	39.650	91.122	1.00	26.27
ATOM	584	C	PRO	A	86	28.721	40.513	90.733	1.00	22.75
ATOM	585	O	PRO	A	86	29.830	40.064	90.530	1.00	22.43
ATOM	586	CB	PRO	A	86	27.873	39.029	92.493	1.00	27.52
ATOM	587	CG	PRO	A	86	27.284	37.627	92.399	1.00	27.61
ATOM	588	CD	PRO	A	86	27.591	37.258	90.945	1.00	31.08
ATOM	589	N	ILE	A	87	28.350	41.776	90.659	1.00	22.99
ATOM	590	CA	ILE	A	87	29.363	42.816	90.469	1.00	24.80
ATOM	591	C	ILE	A	87	29.642	43.494	91.811	1.00	25.76
ATOM	592	O	ILE	A	87	28.956	44.424	92.220	1.00	24.68
ATOM	593	CB	ILE	A	87	28.908	43.860	89.427	1.00	24.26
ATOM	594	CG1	ILE	A	87	28.626	43.165	88.076	1.00	23.29

[Drawing 21]

ATOM	595	CG2	ILE	A	87	29.997	44.923	89.306	1.00	23.62
ATOM	596	CD1	ILE	A	87	27.925	44.100	87.092	1.00	21.95
ATOM	597	N	THR	A	88	30.655	42.914	92.481	1.00	25.86
ATOM	598	CA	THR	A	88	30.925	43.247	93.903	1.00	25.48
ATOM	599	C	THR	A	88	32.418	43.249	94.166	1.00	25.25
ATOM	600	O	THR	A	88	33.131	42.561	93.445	1.00	24.26
ATOM	601	CB	THR	A	88	30.332	42.211	94.859	1.00	22.31
ATOM	602	OG1	THR	A	88	31.102	41.029	94.702	1.00	25.42
ATOM	603	CG2	THR	A	88	28.833	41.943	94.710	1.00	19.45
ATOM	604	N	GLU	A	89	32.891	43.970	95.204	1.00	26.63
ATOM	605	CA	GLU	A	89	34.322	43.845	95.577	1.00	25.29
ATOM	606	C	GLU	A	89	34.810	42.429	95.889	1.00	25.30
ATOM	607	O	GLU	A	89	35.924	41.999	95.611	1.00	26.30
ATOM	608	CB	GLU	A	89	34.652	44.773	96.741	1.00	25.64
ATOM	609	CG	GLU	A	89	34.334	46.193	96.340	1.00	26.52
ATOM	610	CD	GLU	A	89	34.551	47.228	97.414	1.00	29.70
ATOM	611	OE1	GLU	A	89	35.136	48.245	97.123	1.00	33.05
ATOM	612	OE2	GLU	A	89	34.138	47.077	98.540	1.00	27.59
ATOM	613	N	LYS	A	90	33.860	41.697	96.459	1.00	26.25
ATOM	614	CA	LYS	A	90	34.095	40.310	96.883	1.00	28.81
ATOM	615	C	LYS	A	90	34.285	39.313	95.780	1.00	28.19
ATOM	616	O	LYS	A	90	35.206	38.518	95.773	1.00	30.49
ATOM	617	CB	LYS	A	90	32.889	39.869	97.672	1.00	31.00
ATOM	618	CG	LYS	A	90	32.956	38.478	98.228	1.00	37.00
ATOM	619	CD	LYS	A	90	31.536	38.026	98.503	1.00	43.53
ATOM	620	CE	LYS	A	90	31.386	36.504	98.712	1.00	50.17
ATOM	621	NZ	LYS	A	90	32.257	35.875	97.701	1.00	60.80
ATOM	622	N	ASP	A	91	33.324	39.416	94.870	1.00	28.68
ATOM	623	CA	ASP	A	91	33.271	38.504	93.738	1.00	29.34
ATOM	624	C	ASP	A	91	33.911	38.947	92.420	1.00	29.37
ATOM	625	O	ASP	A	91	34.429	38.173	91.635	1.00	31.54
ATOM	626	CB	ASP	A	91	31.827	38.162	93.438	1.00	30.91
ATOM	627	CG	ASP	A	91	31.087	37.722	94.674	1.00	31.69
ATOM	628	OD1	ASP	A	91	31.395	36.657	95.212	1.00	35.66
ATOM	629	OD2	ASP	A	91	30.186	38.438	95.088	1.00	29.63
ATOM	630	N	ALA	A	92	33.830	40.240	92.165	1.00	28.62
ATOM	631	CA	ALA	A	92	34.443	40.713	90.919	1.00	26.75
ATOM	632	C	ALA	A	92	35.255	41.981	91.131	1.00	26.94
ATOM	633	O	ALA	A	92	34.937	43.081	90.690	1.00	26.94
ATOM	634	CB	ALA	A	92	33.390	40.934	89.817	1.00	23.93
ATOM	635	N	PRO	A	93	36.336	41.826	91.930	1.00	27.16
ATOM	636	CA	PRO	A	93	37.151	43.015	92.274	1.00	25.78
ATOM	637	C	PRO	A	93	37.832	43.865	91.160	1.00	24.62
ATOM	638	O	PRO	A	93	37.844	45.098	91.178	1.00	22.75
ATOM	639	CB	PRO	A	93	38.120	42.411	93.292	1.00	25.31
ATOM	640	CG	PRO	A	93	38.219	40.926	92.945	1.00	23.54
ATOM	641	CD	PRO	A	93	36.817	40.578	92.534	1.00	25.29
ATOM	642	N	ALA	A	94	38.409	43.174	90.170	1.00	25.16
ATOM	643	CA	ALA	A	94	38.954	43.886	89.005	1.00	23.77
ATOM	644	C	ALA	A	94	37.923	44.715	88.249	1.00	17.72
ATOM	645	O	ALA	A	94	38.116	45.897	88.005	1.00	19.91
ATOM	646	CB	ALA	A	94	39.676	42.931	88.058	1.00	21.52
ATOM	647	N	LEU	A	95	36.787	44.081	88.026	1.00	19.68
ATOM	648	CA	LEU	A	95	35.577	44.770	87.539	1.00	20.23

[Drawing 22]

ATOM	649	C	LEU	A	95	35.001	45.902	88.385	1.00	21.85
ATOM	650	O	LEU	A	95	34.809	47.026	87.943	1.00	21.66
ATOM	651	CB	LEU	A	95	34.466	43.755	87.271	1.00	20.70
ATOM	652	CG	LEU	A	95	33.250	44.285	86.467	1.00	21.32
ATOM	653	CD1	LEU	A	95	32.299	43.149	86.063	1.00	20.10
ATOM	654	CD2	LEU	A	95	33.698	45.111	85.240	1.00	20.93
ATOM	655	N	HIS	A	96	34.755	45.606	89.667	1.00	21.70
ATOM	656	CA	HIS	A	96	34.313	46.691	90.543	1.00	17.84
ATOM	657	C	HIS	A	96	35.214	47.924	90.580	1.00	17.76
ATOM	658	O	HIS	A	96	34.767	49.069	90.496	1.00	19.44
ATOM	659	CB	HIS	A	96	34.042	46.116	91.937	1.00	20.62
ATOM	660	CG	HIS	A	96	32.934	46.893	92.613	1.00	21.96
ATOM	661	ND1	HIS	A	96	33.021	48.094	93.229	1.00	21.34
ATOM	662	CD2	HIS	A	96	31.614	46.470	92.680	1.00	24.62
ATOM	663	CE1	HIS	A	96	31.790	48.442	93.690	1.00	18.16
ATOM	664	NE2	HIS	A	96	30.923	47.437	93.338	1.00	23.59
ATOM	665	N	LYS	A	97	36.539	47.639	90.629	1.00	18.11
ATOM	666	CA	LYS	A	97	37.544	48.713	90.581	1.00	18.50
ATOM	667	C	LYS	A	97	37.519	49.564	89.317	1.00	20.80
ATOM	668	O	LYS	A	97	37.452	50.781	89.373	1.00	21.08
ATOM	669	CB	LYS	A	97	38.924	48.085	90.766	1.00	17.26
ATOM	670	CG	LYS	A	97	40.125	49.014	90.594	1.00	21.24
ATOM	671	CD	LYS	A	97	40.283	50.213	91.525	1.00	30.10
ATOM	672	CE	LYS	A	97	41.482	51.160	91.164	1.00	33.55
ATOM	673	NZ	LYS	A	97	41.557	52.449	91.915	1.00	29.55
ATOM	674	N	LEU	A	98	37.532	48.857	88.155	1.00	22.36
ATOM	675	CA	LEU	A	98	37.291	49.555	86.851	1.00	22.04
ATOM	676	C	LEU	A	98	36.128	50.581	86.806	1.00	17.59
ATOM	677	O	LEU	A	98	36.223	51.763	86.522	1.00	18.13
ATOM	678	CB	LEU	A	98	37.025	48.477	85.780	1.00	21.44
ATOM	679	CG	LEU	A	98	36.766	49.042	84.375	1.00	20.93
ATOM	680	CD1	LEU	A	98	36.265	47.902	83.493	1.00	22.92
ATOM	681	CD2	LEU	A	98	37.963	49.801	83.811	1.00	18.27
ATOM	682	N	LEU	A	99	34.977	50.024	87.188	1.00	19.16
ATOM	683	CA	LEU	A	99	33.753	50.802	87.186	1.00	18.37
ATOM	684	C	LEU	A	99	33.644	51.930	88.169	1.00	20.61
ATOM	685	O	LEU	A	99	33.068	52.964	87.883	1.00	18.31
ATOM	686	CB	LEU	A	99	32.545	49.874	87.263	1.00	18.90
ATOM	687	CG	LEU	A	99	32.428	48.860	86.191	1.00	20.87
ATOM	688	CD1	LEU	A	99	32.464	49.503	84.841	1.00	14.73
ATOM	689	CD2	LEU	A	99	31.190	48.099	86.497	1.00	19.82
ATOM	690	N	THR	A	100	34.252	51.692	89.359	1.00	22.03
ATOM	691	CA	THR	A	100	34.357	52.777	90.360	1.00	19.41
ATOM	692	C	THR	A	100	35.259	53.938	89.957	1.00	16.72
ATOM	693	O	THR	A	100	34.984	55.118	90.136	1.00	16.55
ATOM	694	CB	THR	A	100	34.889	52.174	91.674	1.00	19.50
ATOM	695	OG1	THR	A	100	34.030	51.113	92.091	1.00	19.99
ATOM	696	CG2	THR	A	100	35.092	53.221	92.758	1.00	21.12
ATOM	697	N	ASN	A	101	36.397	53.537	89.358	1.00	20.56
ATOM	698	CA	ASN	A	101	37.415	54.515	88.998	1.00	19.91
ATOM	699	C	ASN	A	101	37.022	55.479	87.873	1.00	21.88
ATOM	700	O	ASN	A	101	37.610	56.546	87.711	1.00	22.38
ATOM	701	CB	ASN	A	101	38.692	53.763	88.716	1.00	20.98
ATOM	702	CG	ASN	A	101	39.950	54.556	89.041	1.00	22.36

[Drawing 23]

ATOM	703	OD1	ASN	A	101	40.938	53.978	89.459	1.00	30.43
ATOM	704	ND2	ASN	A	101	39.964	55.868	88.889	1.00	23.45
ATOM	705	N	MET	A	102	35.952	55.090	87.154	1.00	21.94
ATOM	706	CA	MET	A	102	35.407	55.984	86.103	1.00	22.28
ATOM	707	C	MET	A	102	34.142	56.755	86.455	1.00	22.36
ATOM	708	O	MET	A	102	33.571	57.482	85.638	1.00	23.37
ATOM	709	CB	MET	A	102	35.162	55.213	84.781	1.00	19.03
ATOM	710	CG	MET	A	102	34.239	54.001	84.972	1.00	18.05
ATOM	711	SD	MET	A	102	33.744	53.082	83.481	1.00	20.07
ATOM	712	CE	MET	A	102	32.429	54.165	83.010	1.00	16.04
ATOM	713	N	ILE	A	103	33.681	56.555	87.724	1.00	21.00
ATOM	714	CA	ILE	A	103	32.441	57.221	88.180	1.00	18.78
ATOM	715	C	ILE	A	103	32.371	58.697	87.833	1.00	17.38
ATOM	716	O	ILE	A	103	31.413	59.152	87.245	1.00	18.08
ATOM	717	CB	ILE	A	103	32.174	57.025	89.732	1.00	16.18
ATOM	718	CG1	ILE	A	103	31.696	55.603	90.031	1.00	19.21
ATOM	719	CG2	ILE	A	103	31.135	58.037	90.272	1.00	12.63
ATOM	720	CD1	ILE	A	103	31.708	55.185	91.522	1.00	17.58
ATOM	721	N	GLU	A	104	33.426	59.429	88.218	1.00	18.81
ATOM	722	CA	GLU	A	104	33.369	60.900	88.092	1.00	18.36
ATOM	723	C	GLU	A	104	33.828	61.520	86.772	1.00	19.60
ATOM	724	O	GLU	A	104	33.420	62.606	86.365	1.00	19.13
ATOM	725	CB	GLU	A	104	34.092	61.600	89.241	1.00	18.56
ATOM	726	CG	GLU	A	104	33.446	61.448	90.617	1.00	19.21
ATOM	727	CD	GLU	A	104	31.994	61.944	90.665	1.00	23.36
ATOM	728	OE1	GLU	A	104	31.225	61.359	91.382	1.00	26.94
ATOM	729	OE2	GLU	A	104	31.574	62.888	90.013	1.00	28.46
ATOM	730	N	ASP	A	105	34.606	60.713	86.049	1.00	18.95
ATOM	731	CA	ASP	A	105	34.743	60.936	84.587	1.00	17.40
ATOM	732	C	ASP	A	105	33.378	61.099	83.886	1.00	15.12
ATOM	733	O	ASP	A	105	33.104	62.102	83.234	1.00	18.61
ATOM	734	CB	ASP	A	105	35.429	59.743	83.951	1.00	16.81
ATOM	735	CG	ASP	A	105	36.831	59.545	84.440	1.00	15.10
ATOM	736	OD1	ASP	A	105	37.573	60.520	84.573	1.00	19.01
ATOM	737	OD2	ASP	A	105	37.177	58.402	84.685	1.00	15.56
ATOM	738	N	ALA	A	106	32.500	60.091	84.096	1.00	15.05
ATOM	739	CA	ALA	A	106	31.111	60.157	83.607	1.00	15.61
ATOM	740	C	ALA	A	106	30.166	61.126	84.315	1.00	19.62
ATOM	741	O	ALA	A	106	29.409	61.881	83.720	1.00	18.83
ATOM	742	CB	ALA	A	106	30.467	58.782	83.682	1.00	11.73
ATOM	743	N	GLY	A	107	30.263	61.102	85.674	1.00	21.49
ATOM	744	CA	GLY	A	107	29.323	61.899	86.503	1.00	16.83
ATOM	745	C	GLY	A	107	29.599	63.356	86.594	1.00	14.80
ATOM	746	O	GLY	A	107	28.714	64.204	86.575	1.00	17.67
ATOM	747	N	ASP	A	108	30.899	63.611	86.662	1.00	16.37
ATOM	748	CA	ASP	A	108	31.305	65.002	86.772	1.00	17.18
ATOM	749	C	ASP	A	108	31.877	65.572	85.485	1.00	18.56
ATOM	750	O	ASP	A	108	31.324	66.472	84.877	1.00	18.77
ATOM	751	CB	ASP	A	108	32.282	65.144	87.947	1.00	16.92
ATOM	752	CG	ASP	A	108	32.862	66.530	88.143	1.00	21.34
ATOM	753	OD1	ASP	A	108	32.247	67.528	87.812	1.00	23.69
ATOM	754	OD2	ASP	A	108	33.983	66.642	88.614	1.00	27.32
ATOM	755	N	LEU	A	109	33.049	65.065	85.107	1.00	18.48
ATOM	756	CA	LEU	A	109	33.814	65.703	84.005	1.00	20.77

[Drawing 24]

ATOM	757	C	LEU A 109	32.954	65.922	82.752	1.00	21.46
ATOM	758	O	LEU A 109	32.905	67.026	82.199	1.00	23.24
ATOM	759	CB	LEU A 109	35.024	64.826	83.679	1.00	20.60
ATOM	760	CG	LEU A 109	36.393	65.285	84.113	1.00	21.65
ATOM	761	CD1	LEU A 109	37.408	64.213	84.096	1.00	17.20
ATOM	762	CD2	LEU A 109	36.469	66.186	85.254	1.00	20.25
ATOM	763	N	ALA A 110	32.206	64.812	82.422	1.00	21.81
ATOM	764	CA	ALA A 110	31.336	64.771	81.215	1.00	20.79
ATOM	765	C	ALA A 110	30.074	65.608	81.232	1.00	23.23
ATOM	766	O	ALA A 110	29.504	65.885	80.182	1.00	23.66
ATOM	767	CB	ALA A 110	30.921	63.333	80.868	1.00	20.49
ATOM	768	N	THR A 111	29.672	66.038	82.465	1.00	20.15
ATOM	769	CA	THR A 111	28.453	66.863	82.653	1.00	19.21
ATOM	770	C	THR A 111	28.654	68.292	83.132	1.00	18.58
ATOM	771	O	THR A 111	27.754	69.106	83.131	1.00	18.77
ATOM	772	CB	THR A 111	27.469	66.257	83.628	1.00	18.46
ATOM	773	OG1	THR A 111	28.011	66.399	84.949	1.00	23.25
ATOM	774	CG2	THR A 111	27.094	64.802	83.347	1.00	15.78
ATOM	775	N	ARG A 112	29.870	68.595	83.547	1.00	20.94
ATOM	776	CA	ARG A 112	30.068	69.805	84.369	1.00	22.62
ATOM	777	C	ARG A 112	29.745	71.185	83.786	1.00	23.68
ATOM	778	O	ARG A 112	29.035	72.025	84.325	1.00	21.09
ATOM	779	CB	ARG A 112	31.512	69.782	84.911	1.00	22.88
ATOM	780	CG	ARG A 112	31.847	70.852	85.952	1.00	22.67
ATOM	781	CD	ARG A 112	33.319	70.922	86.319	1.00	18.55
ATOM	782	NE	ARG A 112	33.831	69.709	86.930	1.00	22.11
ATOM	783	CZ	ARG A 112	35.138	69.496	86.853	1.00	21.99
ATOM	784	NH1	ARG A 112	35.949	70.322	86.227	1.00	23.29
ATOM	785	NH2	ARG A 112	35.623	68.436	87.414	1.00	23.83
ATOM	786	N	SER A 113	30.323	71.398	82.583	1.00	21.66
ATOM	787	CA	SER A 113	30.146	72.736	81.981	1.00	19.14
ATOM	788	C	SER A 113	28.721	73.124	81.629	1.00	20.09
ATOM	789	O	SER A 113	28.288	74.263	81.806	1.00	23.06
ATOM	790	CB	SER A 113	31.029	72.919	80.732	1.00	24.64
ATOM	791	OG	SER A 113	30.812	71.854	79.778	1.00	25.18
ATOM	792	N	ALA A 114	27.955	72.094	81.186	1.00	19.43
ATOM	793	CA	ALA A 114	26.510	72.272	80.944	1.00	17.15
ATOM	794	C	ALA A 114	25.695	72.377	82.247	1.00	16.95
ATOM	795	O	ALA A 114	24.890	73.293	82.402	1.00	17.79
ATOM	796	CB	ALA A 114	25.935	71.096	80.117	1.00	15.05
ATOM	797	N	LYS A 115	25.993	71.462	83.200	1.00	18.76
ATOM	798	CA	LYS A 115	25.431	71.618	84.559	1.00	20.52
ATOM	799	C	LYS A 115	25.524	73.029	85.143	1.00	18.24
ATOM	800	O	LYS A 115	24.535	73.710	85.429	1.00	19.61
ATOM	801	CB	LYS A 115	26.048	70.606	85.508	1.00	17.41
ATOM	802	CG	LYS A 115	25.304	69.294	85.482	1.00	22.93
ATOM	803	CD	LYS A 115	25.867	68.477	86.654	1.00	26.73
ATOM	804	CE	LYS A 115	25.353	67.039	86.850	1.00	26.14
ATOM	805	NZ	LYS A 115	23.888	67.023	87.009	1.00	26.36
ATOM	806	N	ASP A 116	26.784	73.454	85.203	1.00	19.25
ATOM	807	CA	ASP A 116	27.073	74.739	85.832	1.00	20.02
ATOM	808	C	ASP A 116	26.589	75.938	85.076	1.00	23.51
ATOM	809	O	ASP A 116	26.208	76.967	85.612	1.00	24.69
ATOM	810	CB	ASP A 116	28.573	74.896	86.053	1.00	22.26

[Drawing 25]

ATOM	811	CG	ASP	A	116	29.203	73.871	87.029	1.00	25.80
ATOM	812	OD1	ASP	A	116	28.502	73.085	87.657	1.00	27.77
ATOM	813	OD2	ASP	A	116	30.431	73.847	87.166	1.00	28.44
ATOM	814	N	HIS	A	117	26.596	75.793	83.741	1.00	23.53
ATOM	815	CA	HIS	A	117	26.022	76.894	82.957	1.00	21.71
ATOM	816	C	HIS	A	117	24.496	77.044	83.026	1.00	20.75
ATOM	817	O	HIS	A	117	23.932	78.108	83.223	1.00	20.51
ATOM	818	CB	HIS	A	117	26.536	76.787	81.501	1.00	22.93
ATOM	819	CG	HIS	A	117	25.987	77.909	80.635	1.00	22.08
ATOM	820	ND1	HIS	A	117	26.531	79.128	80.459	1.00	23.33
ATOM	821	CD2	HIS	A	117	24.824	77.852	79.881	1.00	22.30
ATOM	822	CE1	HIS	A	117	25.741	79.836	79.615	1.00	23.49
ATOM	823	NE2	HIS	A	117	24.693	79.041	79.262	1.00	23.57
ATOM	824	N	TYR	A	118	23.825	75.906	82.825	1.00	19.95
ATOM	825	CA	TYR	A	118	22.363	76.013	82.795	1.00	19.91
ATOM	826	C	TYR	A	118	21.711	76.075	84.159	1.00	22.89
ATOM	827	O	TYR	A	118	20.615	76.596	84.278	1.00	22.53
ATOM	828	CB	TYR	A	118	21.702	74.869	82.020	1.00	18.70
ATOM	829	CG	TYR	A	118	22.112	74.964	80.550	1.00	19.86
ATOM	830	CD1	TYR	A	118	21.604	76.030	79.775	1.00	20.81
ATOM	831	CD2	TYR	A	118	22.998	74.004	80.005	1.00	20.19
ATOM	832	CE1	TYR	A	118	21.964	76.104	78.410	1.00	24.18
ATOM	833	CE2	TYR	A	118	23.393	74.097	78.652	1.00	22.07
ATOM	834	CZ	TYR	A	118	22.841	75.133	77.869	1.00	24.85
ATOM	835	OH	TYR	A	118	23.138	75.231	76.525	1.00	25.02
ATOM	836	N	MET	A	119	22.385	75.453	85.158	1.00	22.72
ATOM	837	CA	MET	A	119	21.795	75.408	86.516	1.00	25.49
ATOM	838	C	MET	A	119	20.328	75.033	86.619	1.00	22.79
ATOM	839	O	MET	A	119	19.526	75.639	87.309	1.00	23.65
ATOM	840	CB	MET	A	119	22.009	76.758	87.200	1.00	31.90
ATOM	841	CG	MET	A	119	23.479	77.200	87.296	1.00	41.79
ATOM	842	SD	MET	A	119	23.683	78.779	88.163	1.00	50.25
ATOM	843	CE	MET	A	119	22.932	79.838	86.910	1.00	48.37
ATOM	844	N	ARG	A	120	19.958	74.021	85.840	1.00	21.05
ATOM	845	CA	ARG	A	120	18.529	73.782	85.704	1.00	19.45
ATOM	846	C	ARG	A	120	17.877	73.247	86.989	1.00	16.34
ATOM	847	O	ARG	A	120	18.483	72.369	87.587	1.00	17.21
ATOM	848	CB	ARG	A	120	18.345	72.757	84.558	1.00	16.25
ATOM	849	CG	ARG	A	120	16.913	72.517	84.063	1.00	17.39
ATOM	850	CD	ARG	A	120	16.775	71.558	82.842	1.00	19.83
ATOM	851	NE	ARG	A	120	15.450	71.636	82.189	1.00	20.39
ATOM	852	CZ	ARG	A	120	14.929	70.642	81.479	1.00	12.14
ATOM	853	NH1	ARG	A	120	15.600	69.574	81.259	1.00	12.74
ATOM	854	NH2	ARG	A	120	13.724	70.767	81.007	1.00	15.75
ATOM	855	N	ILE	A	121	16.676	73.723	87.290	1.00	16.46
ATOM	856	CA	ILE	A	121	15.807	73.186	88.360	1.00	22.91
ATOM	857	C	ILE	A	121	15.258	71.795	88.080	1.00	23.50
ATOM	858	O	ILE	A	121	14.648	71.571	87.043	1.00	26.14
ATOM	859	CB	ILE	A	121	14.594	74.134	88.686	1.00	25.98
ATOM	860	CG1	ILE	A	121	14.986	75.592	88.783	1.00	29.16
ATOM	861	CG2	ILE	A	121	13.793	73.870	89.982	1.00	23.20
ATOM	862	CD1	ILE	A	121	16.075	75.914	89.785	1.00	29.73
ATOM	863	N	ARG	A	122	15.463	70.877	89.036	1.00	21.01
ATOM	864	CA	ARG	A	122	14.883	69.534	88.976	1.00	19.80

[Drawing 26]



ATOM	865	C	ARG A 122	13.372	69.532	89.091	1.00	17.61
ATOM	866	O	ARG A 122	12.805	70.488	89.613	1.00	18.79
ATOM	867	CB	ARG A 122	15.533	68.653	90.033	1.00	17.47
ATOM	868	CG	ARG A 122	17.023	68.706	89.841	1.00	18.78
ATOM	869	CD	ARG A 122	17.721	67.861	90.852	1.00	21.00
ATOM	870	NE	ARG A 122	19.141	68.121	90.748	1.00	28.80
ATOM	871	CZ	ARG A 122	19.914	67.081	90.491	1.00	34.31
ATOM	872	NH1	ARG A 122	19.401	65.871	90.426	1.00	40.28
ATOM	873	NH2	ARG A 122	21.196	67.257	90.289	1.00	32.47
ATOM	874	N	PRO A 123	12.700	68.460	88.577	1.00	17.64
ATOM	875	CA	PRO A 123	11.243	68.461	88.684	1.00	18.56
ATOM	876	C	PRO A 123	10.668	68.630	90.118	1.00	20.86
ATOM	877	O	PRO A 123	9.881	69.536	90.331	1.00	20.65
ATOM	878	CB	PRO A 123	10.808	67.150	88.004	1.00	16.86
ATOM	879	CG	PRO A 123	12.028	66.572	87.296	1.00	15.55
ATOM	880	CD	PRO A 123	13.235	67.291	87.881	1.00	15.48
ATOM	881	N	PHE A 124	11.077	67.771	91.105	1.00	21.82
ATOM	882	CA	PHE A 124	10.489	67.948	92.468	1.00	20.01
ATOM	883	C	PHE A 124	10.541	69.394	93.016	1.00	16.73
ATOM	884	O	PHE A 124	9.581	69.970	93.486	1.00	17.82
ATOM	885	CB	PHE A 124	11.044	66.869	93.422	1.00	17.84
ATOM	886	CG	PHE A 124	12.484	67.199	93.795	1.00	19.87
ATOM	887	CD1	PHE A 124	12.748	68.117	94.850	1.00	20.96
ATOM	888	CD2	PHE A 124	13.554	66.632	93.075	1.00	19.87
ATOM	889	CE1	PHE A 124	14.068	68.524	95.134	1.00	21.78
ATOM	890	CE2	PHE A 124	14.881	67.014	93.381	1.00	21.98
ATOM	891	CZ	PHE A 124	15.129	67.975	94.386	1.00	23.27
ATOM	892	N	ALA A 125	11.681	70.039	92.775	1.00	18.30
ATOM	893	CA	ALA A 125	11.866	71.464	93.089	1.00	20.06
ATOM	894	C	ALA A 125	11.033	72.481	92.291	1.00	24.90
ATOM	895	O	ALA A 125	10.455	73.445	92.789	1.00	24.77
ATOM	896	CB	ALA A 125	13.358	71.840	92.990	1.00	16.96
ATOM	897	N	PHE A 126	10.941	72.202	90.977	1.00	23.91
ATOM	898	CA	PHE A 126	10.017	72.958	90.145	1.00	22.66
ATOM	899	C	PHE A 126	8.590	72.919	90.692	1.00	20.74
ATOM	900	O	PHE A 126	7.910	73.945	90.785	1.00	21.66
ATOM	901	CB	PHE A 126	10.051	72.379	88.705	1.00	19.61
ATOM	902	CG	PHE A 126	9.147	73.140	87.765	1.00	16.99
ATOM	903	CD1	PHE A 126	9.669	74.211	87.022	1.00	15.15
ATOM	904	CD2	PHE A 126	7.794	72.757	87.656	1.00	17.75
ATOM	905	CE1	PHE A 126	8.824	74.913	86.144	1.00	14.16
ATOM	906	CE2	PHE A 126	6.940	73.472	86.799	1.00	17.56
ATOM	907	CZ	PHE A 126	7.471	74.538	86.048	1.00	12.93
ATOM	908	N	TYR A 127	8.183	71.664	91.002	1.00	20.13
ATOM	909	CA	TYR A 127	6.843	71.414	91.525	1.00	20.41
ATOM	910	C	TYR A 127	6.642	71.689	93.032	1.00	24.41
ATOM	911	O	TYR A 127	5.525	71.665	93.532	1.00	23.70
ATOM	912	CB	TYR A 127	6.370	69.994	91.207	1.00	20.85
ATOM	913	CG	TYR A 127	6.198	69.850	89.697	1.00	25.51
ATOM	914	CD1	TYR A 127	7.200	69.185	88.947	1.00	27.02
ATOM	915	CD2	TYR A 127	5.064	70.407	89.065	1.00	25.24
ATOM	916	CE1	TYR A 127	7.057	69.037	87.552	1.00	28.75
ATOM	917	CE2	TYR A 127	4.907	70.261	87.663	1.00	28.24
ATOM	918	CZ	TYR A 127	5.891	69.543	86.936	1.00	28.76

[Drawing 27]

ATOM	919	OH	TYR	A	127	5.716	69.314	85.588	1.00	27.53
ATOM	920	N	GLY	A	128	7.764	71.960	93.723	1.00	23.74
ATOM	921	CA	GLY	A	128	7.675	72.217	95.170	1.00	24.88
ATOM	922	C	GLY	A	128	7.138	71.011	95.924	1.00	24.57
ATOM	923	O	GLY	A	128	6.383	71.095	96.866	1.00	29.82
ATOM	924	N	VAL	A	129	7.527	69.854	95.426	1.00	24.16
ATOM	925	CA	VAL	A	129	7.144	68.604	96.044	1.00	23.21
ATOM	926	C	VAL	A	129	8.377	67.802	96.358	1.00	24.99
ATOM	927	O	VAL	A	129	9.529	68.188	96.189	1.00	25.90
ATOM	928	CB	VAL	A	129	6.193	67.776	95.187	1.00	22.38
ATOM	929	CG1	VAL	A	129	6.738	67.390	93.815	1.00	17.75
ATOM	930	CG2	VAL	A	129	4.895	68.549	95.125	1.00	24.52
ATOM	931	N	SER	A	130	8.089	66.617	96.832	1.00	25.98
ATOM	932	CA	SER	A	130	9.242	65.724	96.973	1.00	29.71
ATOM	933	C	SER	A	130	9.322	64.672	95.895	1.00	29.73
ATOM	934	O	SER	A	130	8.403	64.485	95.103	1.00	30.28
ATOM	935	CB	SER	A	130	9.183	64.999	98.309	1.00	35.36
ATOM	936	OG	SER	A	130	7.964	64.244	98.427	1.00	41.61
ATOM	937	N	THR	A	131	10.440	63.952	95.934	1.00	30.35
ATOM	938	CA	THR	A	131	10.533	62.819	94.996	1.00	27.90
ATOM	939	C	THR	A	131	9.733	61.569	95.361	1.00	28.80
ATOM	940	O	THR	A	131	9.051	61.508	96.366	1.00	30.16
ATOM	941	CB	THR	A	131	11.996	62.471	94.783	1.00	26.62
ATOM	942	OG1	THR	A	131	12.500	61.841	95.953	1.00	29.21
ATOM	943	CG2	THR	A	131	12.839	63.682	94.446	1.00	19.32
ATOM	944	N	CYS	A	132	9.835	60.528	94.551	1.00	27.12
ATOM	945	CA	CYS	A	132	9.203	59.271	94.996	1.00	27.75
ATOM	946	C	CYS	A	132	9.911	58.540	96.137	1.00	28.96
ATOM	947	O	CYS	A	132	9.556	57.487	96.634	1.00	28.80
ATOM	948	CB	CYS	A	132	9.081	58.274	93.831	1.00	24.68
ATOM	949	SG	CYS	A	132	10.538	57.273	93.459	1.00	24.12
ATOM	950	N	ASN	A	133	11.021	59.158	96.447	1.00	33.31
ATOM	951	CA	ASN	A	133	12.012	58.492	97.236	1.00	39.44
ATOM	952	C	ASN	A	133	12.008	58.776	98.750	1.00	45.19
ATOM	953	O	ASN	A	133	12.269	57.928	99.583	1.00	50.38
ATOM	954	CB	ASN	A	133	13.285	58.876	96.522	1.00	35.83
ATOM	955	CG	ASN	A	133	14.294	57.823	96.731	1.00	37.18
ATOM	956	OD1	ASN	A	133	15.478	58.059	96.663	1.00	38.83
ATOM	957	ND2	ASN	A	133	13.815	56.623	97.017	1.00	42.51
ATOM	958	N	THR	A	134	11.642	59.993	99.118	1.00	48.69
ATOM	959	CA	THR	A	134	12.585	61.110	98.925	1.00	56.17
ATOM	960	C	THR	A	134	13.935	61.171	99.735	1.00	61.49
ATOM	961	OCT1	THR	A	134	14.052	60.565	100.816	1.00	66.36
ATOM	962	OCT2	THR	A	134	14.937	61.779	99.291	1.00	63.18
ATOM	963	CB	THR	A	134	11.704	62.374	98.968	1.00	56.04
ATOM	964	OG1	THR	A	134	12.306	63.614	98.469	1.00	56.23
ATOM	965	CG2	THR	A	134	10.869	62.400	100.243	1.00	53.77
ATOM	966	N	GLN	A	137	16.953	60.437	100.819	1.00	100.00
ATOM	967	CA	GLN	A	137	17.845	60.498	102.027	1.00	99.78
ATOM	968	C	GLN	A	137	19.036	61.512	102.211	1.00	98.61
ATOM	969	O	GLN	A	137	19.386	61.891	103.324	1.00	97.54
ATOM	970	CB	GLN	A	137	18.343	59.083	102.397	1.00	100.00
ATOM	971	CG	GLN	A	137	17.669	58.407	103.615	1.00	99.38
ATOM	972	CD	GLN	A	137	18.060	59.017	104.963	1.00	98.64

[Drawing 28]

ATOM	973	OE1	GLN	A	137	17.484	58.784	106.009	1.00	98.03
ATOM	974	NE2	GLN	A	137	19.086	59.847	104.972	1.00	100.00
ATOM	975	N	ASP	A	138	19.627	61.949	101.081	1.00	97.91
ATOM	976	CA	ASP	A	138	20.479	63.151	101.162	1.00	95.99
ATOM	977	C	ASP	A	138	19.761	64.494	101.063	1.00	93.86
ATOM	978	O	ASP	A	138	18.589	64.579	100.711	1.00	92.76
ATOM	979	CB	ASP	A	138	21.585	63.102	100.115	1.00	97.46
ATOM	980	CG	ASP	A	138	22.893	62.963	100.866	1.00	100.00
ATOM	981	OD1	ASP	A	138	23.371	61.842	101.028	1.00	100.00
ATOM	982	OD2	ASP	A	138	23.432	63.969	101.333	1.00	100.00
ATOM	983	N	LYS	A	139	20.494	65.564	101.380	1.00	92.69
ATOM	984	CA	LYS	A	139	19.813	66.855	101.218	1.00	91.50
ATOM	985	C	LYS	A	139	19.719	67.313	99.775	1.00	88.92
ATOM	986	O	LYS	A	139	20.557	68.082	99.308	1.00	89.47
ATOM	987	CB	LYS	A	139	20.464	67.987	102.010	1.00	94.21
ATOM	988	CG	LYS	A	139	19.574	69.246	102.020	1.00	96.82
ATOM	989	CD	LYS	A	139	20.362	70.569	102.123	1.00	99.43
ATOM	990	CE	LYS	A	139	20.785	71.241	100.793	1.00	100.00
ATOM	991	NZ	LYS	A	139	21.686	70.402	99.978	1.00	100.00
ATOM	992	N	LEU	A	140	18.654	66.828	99.114	1.00	85.87
ATOM	993	CA	LEU	A	140	18.426	67.018	97.660	1.00	79.60
ATOM	994	C	LEU	A	140	18.772	68.392	97.043	1.00	75.62
ATOM	995	O	LEU	A	140	18.242	69.442	97.416	1.00	75.74
ATOM	996	CB	LEU	A	140	16.981	66.620	97.283	1.00	77.27
ATOM	997	CG	LEU	A	140	16.640	65.142	97.462	1.00	74.31
ATOM	998	CD1	LEU	A	140	17.569	64.263	96.645	1.00	73.21
ATOM	999	CD2	LEU	A	140	15.178	64.838	97.167	1.00	73.91
ATOM	1000	N	SER	A	141	19.713	68.357	96.067	1.00	70.08
ATOM	1001	CA	SER	A	141	19.868	69.619	95.320	1.00	64.86
ATOM	1002	C	SER	A	141	18.713	69.941	94.396	1.00	61.18
ATOM	1003	O	SER	A	141	18.189	69.080	93.708	1.00	61.77
ATOM	1004	CB	SER	A	141	21.127	69.682	94.461	1.00	64.49
ATOM	1005	OG	SER	A	141	21.354	71.028	94.002	1.00	66.43
ATOM	1006	N	LYS	A	142	18.349	71.235	94.379	1.00	57.81
ATOM	1007	CA	LYS	A	142	17.238	71.661	93.493	1.00	54.35
ATOM	1008	C	LYS	A	142	17.498	71.829	91.964	1.00	45.94
ATOM	1009	O	LYS	A	142	16.615	72.091	91.202	1.00	40.89
ATOM	1010	CB	LYS	A	142	16.631	72.953	94.061	1.00	57.69
ATOM	1011	CG	LYS	A	142	17.518	74.222	93.959	1.00	62.63
ATOM	1012	CD	LYS	A	142	16.625	75.420	93.545	1.00	68.07
ATOM	1013	CE	LYS	A	142	17.200	76.856	93.475	1.00	71.28
ATOM	1014	NZ	LYS	A	142	16.136	77.844	93.162	1.00	70.88
ATOM	1015	N	ASN	A	143	18.772	71.719	91.611	1.00	45.99
ATOM	1016	CA	ASN	A	143	19.527	72.392	90.538	1.00	44.71
ATOM	1017	C	ASN	A	143	20.592	71.481	89.878	1.00	42.57
ATOM	1018	O	ASN	A	143	20.794	70.322	90.283	1.00	40.17
ATOM	1019	CB	ASN	A	143	20.343	73.547	91.124	1.00	50.34
ATOM	1020	CG	ASN	A	143	19.624	74.818	90.876	1.00	55.19
ATOM	1021	OD1	ASN	A	143	18.441	74.944	91.098	1.00	59.21
ATOM	1022	ND2	ASN	A	143	20.366	75.786	90.389	1.00	59.88
ATOM	1023	N	GLY	A	144	21.265	72.084	88.819	1.00	39.72
ATOM	1024	CA	GLY	A	144	22.264	71.401	87.958	1.00	26.74
ATOM	1025	C	GLY	A	144	21.691	70.105	87.407	1.00	21.44
ATOM	1026	O	GLY	A	144	22.343	69.071	87.322	1.00	25.78

[Drawing 29]

ATOM	1027	N	SER A 145	20.380	70.181	87.105	1.00	19.15
ATOM	1028	CA	SER A 145	19.590	69.023	86.596	1.00	20.14
ATOM	1029	C	SER A 145	20.077	68.461	85.223	1.00	20.58
ATOM	1030	O	SER A 145	20.121	67.279	84.943	1.00	21.22
ATOM	1031	CB	SER A 145	18.171	69.499	86.338	1.00	18.89
ATOM	1032	OG	SER A 145	17.219	68.526	86.712	1.00	28.02
ATOM	1033	N	TYR A 146	20.531	69.419	84.399	1.00	22.70
ATOM	1034	CA	TYR A 146	20.867	69.170	82.968	1.00	19.51
ATOM	1035	C	TYR A 146	22.366	69.260	82.633	1.00	16.00
ATOM	1036	O	TYR A 146	22.930	70.339	82.736	1.00	17.85
ATOM	1037	CB	TYR A 146	20.097	70.216	82.114	1.00	18.79
ATOM	1038	CG	TYR A 146	20.211	69.933	80.600	1.00	20.29
ATOM	1039	CD1	TYR A 146	19.310	69.027	80.015	1.00	19.58
ATOM	1040	CD2	TYR A 146	21.205	70.582	79.824	1.00	20.42
ATOM	1041	CE1	TYR A 146	19.389	68.781	78.631	1.00	23.13
ATOM	1042	CE2	TYR A 146	21.287	70.337	78.424	1.00	21.68
ATOM	1043	CZ	TYR A 146	20.349	69.449	77.849	1.00	20.03
ATOM	1044	OH	TYR A 146	20.320	69.236	76.483	1.00	21.40
ATOM	1045	N	PRO A 147	22.994	68.144	82.187	1.00	16.52
ATOM	1046	CA	PRO A 147	22.385	66.793	82.188	1.00	17.87
ATOM	1047	C	PRO A 147	22.496	66.069	83.580	1.00	20.67
ATOM	1048	O	PRO A 147	23.198	66.531	84.480	1.00	22.35
ATOM	1049	CB	PRO A 147	23.250	66.107	81.122	1.00	15.36
ATOM	1050	CG	PRO A 147	24.649	66.716	81.297	1.00	15.06
ATOM	1051	CD	PRO A 147	24.356	68.168	81.630	1.00	16.28
ATOM	1052	N	SER A 148	21.827	64.908	83.662	1.00	18.73
ATOM	1053	CA	SER A 148	21.951	64.019	84.823	1.00	19.51
ATOM	1054	C	SER A 148	23.269	63.281	84.930	1.00	19.93
ATOM	1055	O	SER A 148	23.601	62.439	84.108	1.00	20.09
ATOM	1056	CB	SER A 148	20.828	62.997	84.807	1.00	18.55
ATOM	1057	OG	SER A 148	20.990	61.966	85.780	1.00	19.29
ATOM	1058	N	GLY A 149	24.036	63.618	85.972	1.00	18.26
ATOM	1059	CA	GLY A 149	25.284	62.888	86.231	1.00	16.00
ATOM	1060	C	GLY A 149	25.096	61.411	86.577	1.00	19.38
ATOM	1061	O	GLY A 149	25.791	60.549	86.044	1.00	21.04
ATOM	1062	N	HIS A 150	24.085	61.096	87.427	1.00	20.25
ATOM	1063	CA	HIS A 150	23.690	59.680	87.624	1.00	19.01
ATOM	1064	C	HIS A 150	23.381	58.861	86.330	1.00	19.93
ATOM	1065	O	HIS A 150	23.833	57.725	86.145	1.00	20.78
ATOM	1066	CB	HIS A 150	22.507	59.533	88.619	1.00	18.01
ATOM	1067	CG	HIS A 150	22.162	58.068	88.909	1.00	20.60
ATOM	1068	ND1	HIS A 150	22.864	57.235	89.730	1.00	23.41
ATOM	1069	CD2	HIS A 150	21.117	57.313	88.374	1.00	21.91
ATOM	1070	CE1	HIS A 150	22.287	55.996	89.732	1.00	22.83
ATOM	1071	NE2	HIS A 150	21.220	56.051	88.893	1.00	24.19
ATOM	1072	N	THR A 151	22.593	59.482	85.432	1.00	18.98
ATOM	1073	CA	THR A 151	22.325	58.814	84.132	1.00	17.17
ATOM	1074	C	THR A 151	23.548	58.652	83.228	1.00	13.61
ATOM	1075	O	THR A 151	23.814	57.594	82.659	1.00	17.00
ATOM	1076	CB	THR A 151	21.270	59.590	83.407	1.00	16.57
ATOM	1077	OG1	THR A 151	20.137	59.738	84.258	1.00	18.00
ATOM	1078	CG2	THR A 151	20.898	58.983	82.045	1.00	13.22
ATOM	1079	N	SER A 152	24.361	59.722	83.197	1.00	14.30
ATOM	1080	CA	SER A 152	25.687	59.598	82.557	1.00	15.99

[Drawing 30]

ATOM	1081	C	SER A 152	26.575	58.446	83.029	1.00	19.72
ATOM	1082	O	SER A 152	27.086	57.628	82.255	1.00	17.38
ATOM	1083	CB	SER A 152	26.434	60.927	82.644	1.00	12.58
ATOM	1084	OG	SER A 152	27.648	60.861	81.911	1.00	16.08
ATOM	1085	N	ILE A 153	26.662	58.340	84.403	1.00	20.60
ATOM	1086	CA	ILE A 153	27.272	57.121	85.017	1.00	16.15
ATOM	1087	C	ILE A 153	26.622	55.802	84.631	1.00	10.76
ATOM	1088	O	ILE A 153	27.293	54.850	84.262	1.00	14.38
ATOM	1089	CB	ILE A 153	27.384	57.170	86.608	1.00	15.02
ATOM	1090	CG1	ILE A 153	28.187	58.421	86.963	1.00	16.37
ATOM	1091	CG2	ILE A 153	28.154	55.944	87.164	1.00	12.98
ATOM	1092	CD1	ILE A 153	27.870	59.034	88.338	1.00	16.58
ATOM	1093	N	GLY A 154	25.285	55.763	84.720	1.00	9.72
ATOM	1094	CA	GLY A 154	24.662	54.476	84.397	1.00	13.63
ATOM	1095	C	GLY A 154	24.843	54.033	82.910	1.00	16.00
ATOM	1096	O	GLY A 154	25.022	52.866	82.571	1.00	16.37
ATOM	1097	N	TRP A 155	24.801	55.047	82.025	1.00	16.77
ATOM	1098	CA	TRP A 155	24.960	54.747	80.589	1.00	16.73
ATOM	1099	C	TRP A 155	26.378	54.351	80.200	1.00	15.90
ATOM	1100	O	TRP A 155	26.656	53.301	79.628	1.00	18.41
ATOM	1101	CB	TRP A 155	24.442	55.940	79.771	1.00	16.52
ATOM	1102	CG	TRP A 155	24.320	55.475	78.321	1.00	19.11
ATOM	1103	CD1	TRP A 155	25.009	56.015	77.210	1.00	18.94
ATOM	1104	CD2	TRP A 155	23.471	54.426	77.765	1.00	18.98
ATOM	1105	NE1	TRP A 155	24.679	55.352	76.044	1.00	17.77
ATOM	1106	CE2	TRP A 155	23.781	54.322	76.357	1.00	22.22
ATOM	1107	CE3	TRP A 155	22.585	53.486	78.337	1.00	19.43
ATOM	1108	CZ2	TRP A 155	23.084	53.377	75.564	1.00	17.99
ATOM	1109	CZ3	TRP A 155	21.913	52.538	77.537	1.00	19.46
ATOM	1110	CH2	TRP A 155	22.191	52.464	76.158	1.00	17.84
ATOM	1111	N	ALA A 156	27.299	55.209	80.623	1.00	15.37
ATOM	1112	CA	ALA A 156	28.702	54.836	80.515	1.00	14.36
ATOM	1113	C	ALA A 156	29.156	53.503	81.108	1.00	19.46
ATOM	1114	O	ALA A 156	29.895	52.723	80.528	1.00	19.86
ATOM	1115	CB	ALA A 156	29.564	55.918	81.136	1.00	15.83
ATOM	1116	N	THR A 157	28.651	53.207	82.327	1.00	19.95
ATOM	1117	CA	THR A 157	28.820	51.832	82.831	1.00	17.52
ATOM	1118	C	THR A 157	28.177	50.744	81.994	1.00	15.22
ATOM	1119	O	THR A 157	28.825	49.745	81.765	1.00	19.09
ATOM	1120	CB	THR A 157	28.328	51.667	84.291	1.00	14.92
ATOM	1121	OG1	THR A 157	28.932	52.679	85.054	1.00	18.29
ATOM	1122	CG2	THR A 157	28.620	50.327	84.944	1.00	13.21
ATOM	1123	N	ALA A 158	26.930	50.947	81.535	1.00	14.63
ATOM	1124	CA	ALA A 158	26.365	49.936	80.621	1.00	17.10
ATOM	1125	C	ALA A 158	27.213	49.686	79.354	1.00	15.52
ATOM	1126	O	ALA A 158	27.539	48.565	79.025	1.00	16.52
ATOM	1127	CB	ALA A 158	24.942	50.300	80.203	1.00	13.99
ATOM	1128	N	LEU A 159	27.655	50.766	78.705	1.00	17.91
ATOM	1129	CA	LEU A 159	28.613	50.615	77.580	1.00	17.69
ATOM	1130	C	LEU A 159	29.895	49.851	77.846	1.00	19.93
ATOM	1131	O	LEU A 159	30.277	48.954	77.092	1.00	19.21
ATOM	1132	CB	LEU A 159	28.959	51.971	76.939	1.00	14.08
ATOM	1133	CG	LEU A 159	27.744	52.759	76.396	1.00	11.97
ATOM	1134	CD1	LEU A 159	27.045	52.105	75.210	1.00	12.90

[Drawing 31]

ATOM	1135	CD2	LEU	A	159	28.177	54.158	76.046	1.00	12.40
ATOM	1136	N	VAL	A	160	30.547	50.181	79.014	1.00	21.70
ATOM	1137	CA	VAL	A	160	31.713	49.315	79.310	1.00	20.85
ATOM	1138	C	VAL	A	160	31.429	47.877	79.767	1.00	21.33
ATOM	1139	O	VAL	A	160	32.086	46.918	79.409	1.00	20.74
ATOM	1140	CB	VAL	A	160	32.574	50.032	80.367	1.00	21.59
ATOM	1141	CG1	VAL	A	160	33.518	49.143	81.174	1.00	20.11
ATOM	1142	CG2	VAL	A	160	33.299	51.307	79.977	1.00	20.10
ATOM	1143	N	LEU	A	161	30.351	47.711	80.542	1.00	21.86
ATOM	1144	CA	LEU	A	161	29.850	46.366	80.838	1.00	20.50
ATOM	1145	C	LEU	A	161	29.462	45.490	79.613	1.00	23.16
ATOM	1146	O	LEU	A	161	29.753	44.294	79.564	1.00	22.89
ATOM	1147	CB	LEU	A	161	28.623	46.472	81.733	1.00	18.65
ATOM	1148	CG	LEU	A	161	28.685	46.438	83.262	1.00	20.99
ATOM	1149	CD1	LEU	A	161	27.473	46.378	84.194	1.00	21.43
ATOM	1150	CD2	LEU	A	161	29.729	45.492	83.855	1.00	19.30
ATOM	1151	N	ALA	A	162	28.755	46.146	78.648	1.00	21.20
ATOM	1152	CA	ALA	A	162	28.384	45.496	77.361	1.00	19.14
ATOM	1153	C	ALA	A	162	29.591	44.948	76.586	1.00	17.15
ATOM	1154	O	ALA	A	162	29.620	43.812	76.133	1.00	20.85
ATOM	1155	CB	ALA	A	162	27.581	46.464	76.500	1.00	17.38
ATOM	1156	N	GLU	A	163	30.663	45.745	76.603	1.00	14.74
ATOM	1157	CA	GLU	A	163	31.962	45.262	76.118	1.00	17.48
ATOM	1158	C	GLU	A	163	32.648	44.080	76.824	1.00	22.07
ATOM	1159	O	GLU	A	163	33.271	43.216	76.227	1.00	23.96
ATOM	1160	CB	GLU	A	163	32.915	46.448	76.000	1.00	13.52
ATOM	1161	CG	GLU	A	163	34.227	46.018	75.359	1.00	13.04
ATOM	1162	CD	GLU	A	163	35.240	47.119	75.338	1.00	15.88
ATOM	1163	OE1	GLU	A	163	36.427	46.814	75.269	1.00	19.78
ATOM	1164	OE2	GLU	A	163	34.873	48.290	75.377	1.00	20.10
ATOM	1165	N	ILE	A	164	32.504	44.039	78.153	1.00	20.17
ATOM	1166	CA	ILE	A	164	32.996	42.869	78.905	1.00	18.72
ATOM	1167	C	ILE	A	164	32.164	41.609	78.757	1.00	17.39
ATOM	1168	O	ILE	A	164	32.635	40.481	78.674	1.00	20.44
ATOM	1169	CB	ILE	A	164	33.132	43.293	80.382	1.00	20.67
ATOM	1170	CG1	ILE	A	164	34.222	44.361	80.452	1.00	18.83
ATOM	1171	CG2	ILE	A	164	33.398	42.110	81.345	1.00	20.70
ATOM	1172	CD1	ILE	A	164	34.144	45.084	81.793	1.00	21.31
ATOM	1173	N	ASN	A	165	30.869	41.846	78.704	1.00	18.41
ATOM	1174	CA	ASN	A	165	29.979	40.712	78.524	1.00	21.36
ATOM	1175	C	ASN	A	165	28.957	40.867	77.375	1.00	23.74
ATOM	1176	O	ASN	A	165	27.753	40.988	77.563	1.00	23.14
ATOM	1177	CB	ASN	A	165	29.324	40.404	79.878	1.00	21.69
ATOM	1178	CG	ASN	A	165	28.471	39.156	79.861	1.00	25.72
ATOM	1179	OD1	ASN	A	165	28.469	38.307	78.967	1.00	29.37
ATOM	1180	ND2	ASN	A	165	27.730	39.051	80.951	1.00	27.39
ATOM	1181	N	PRO	A	166	29.466	40.814	76.118	1.00	25.93
ATOM	1182	CA	PRO	A	166	28.556	40.971	74.957	1.00	26.27
ATOM	1183	C	PRO	A	166	27.447	39.924	74.837	1.00	24.06
ATOM	1184	O	PRO	A	166	26.361	40.184	74.360	1.00	24.11
ATOM	1185	CB	PRO	A	166	29.517	41.040	73.781	1.00	25.15
ATOM	1186	CG	PRO	A	166	30.731	40.254	74.255	1.00	27.68
ATOM	1187	CD	PRO	A	166	30.849	40.613	75.728	1.00	24.89
ATOM	1188	N	GLN	A	167	27.679	38.741	75.385	1.00	25.15

[Drawing 32]

ATOM	1189	CA	GLN A 167	26.552	37.804	75.508	1.00	27.09
ATOM	1190	C	GLN A 167	25.275	38.321	76.189	1.00	25.06
ATOM	1191	O	GLN A 167	24.162	37.932	75.883	1.00	23.75
ATOM	1192	CB	GLN A 167	27.080	36.617	76.282	1.00	35.50
ATOM	1193	CG	GLN A 167	27.386	35.380	75.468	1.00	52.12
ATOM	1194	CD	GLN A 167	26.074	34.747	75.000	1.00	65.78
ATOM	1195	OE1	GLN A 167	25.950	34.245	73.889	1.00	72.02
ATOM	1196	NE2	GLN A 167	25.047	34.780	75.867	1.00	71.50
ATOM	1197	N	ARG A 168	25.513	39.242	77.156	1.00	26.04
ATOM	1198	CA	ARG A 168	24.389	39.900	77.837	1.00	25.63
ATOM	1199	C	ARG A 168	24.242	41.368	77.558	1.00	23.88
ATOM	1200	O	ARG A 168	23.632	42.106	78.308	1.00	24.09
ATOM	1201	CB	ARG A 168	24.452	39.638	79.337	1.00	24.63
ATOM	1202	CG	ARG A 168	24.087	38.171	79.408	1.00	25.72
ATOM	1203	CD	ARG A 168	23.986	37.617	80.802	1.00	33.72
ATOM	1204	NE	ARG A 168	22.970	38.302	81.587	1.00	35.38
ATOM	1205	CZ	ARG A 168	21.729	37.877	81.680	1.00	35.91
ATOM	1206	NH1	ARG A 168	20.908	38.482	82.490	1.00	34.99
ATOM	1207	NH2	ARG A 168	21.314	36.867	80.975	1.00	39.28
ATOM	1208	N	GLN A 169	24.838	41.810	76.424	1.00	23.22
ATOM	1209	CA	GLN A 169	24.820	43.228	76.080	1.00	19.99
ATOM	1210	C	GLN A 169	23.441	43.850	76.067	1.00	21.38
ATOM	1211	O	GLN A 169	23.216	44.969	76.492	1.00	24.60
ATOM	1212	CB	GLN A 169	25.571	43.510	74.769	1.00	22.07
ATOM	1213	CG	GLN A 169	24.970	42.878	73.494	1.00	20.93
ATOM	1214	CD	GLN A 169	25.716	43.287	72.207	1.00	23.42
ATOM	1215	OE1	GLN A 169	26.680	44.055	72.202	1.00	24.82
ATOM	1216	NE2	GLN A 169	25.186	42.738	71.109	1.00	13.86
ATOM	1217	N	ASN A 170	22.455	43.089	75.600	1.00	20.48
ATOM	1218	CA	ASN A 170	21.138	43.736	75.525	1.00	20.97
ATOM	1219	C	ASN A 170	20.484	44.007	76.892	1.00	19.73
ATOM	1220	O	ASN A 170	19.852	45.020	77.128	1.00	18.90
ATOM	1221	CB	ASN A 170	20.195	42.930	74.595	1.00	24.43
ATOM	1222	CG	ASN A 170	20.763	42.881	73.153	1.00	25.82
ATOM	1223	OD1	ASN A 170	20.842	43.862	72.440	1.00	26.22
ATOM	1224	ND2	ASN A 170	21.197	41.709	72.734	1.00	25.47
ATOM	1225	N	GLU A 171	20.680	43.042	77.790	1.00	21.27
ATOM	1226	CA	GLU A 171	20.166	43.146	79.157	1.00	19.84
ATOM	1227	C	GLU A 171	20.849	44.220	79.926	1.00	16.23
ATOM	1228	O	GLU A 171	20.199	45.026	80.575	1.00	20.87
ATOM	1229	CB	GLU A 171	20.317	41.822	79.892	1.00	20.47
ATOM	1230	CG	GLU A 171	19.412	40.750	79.312	1.00	24.15
ATOM	1231	CD	GLU A 171	20.157	39.825	78.376	1.00	26.37
ATOM	1232	OE1	GLU A 171	21.076	40.256	77.685	1.00	23.54
ATOM	1233	OE2	GLU A 171	19.801	38.645	78.363	1.00	32.14
ATOM	1234	N	ILE A 172	22.169	44.236	79.751	1.00	17.53
ATOM	1235	CA	ILE A 172	23.029	45.318	80.257	1.00	16.90
ATOM	1236	C	ILE A 172	22.679	46.733	79.813	1.00	20.21
ATOM	1237	O	ILE A 172	22.454	47.636	80.617	1.00	18.91
ATOM	1238	CB	ILE A 172	24.507	44.992	79.956	1.00	17.00
ATOM	1239	CG1	ILE A 172	25.000	43.685	80.613	1.00	15.78
ATOM	1240	CG2	ILE A 172	25.426	46.163	80.300	1.00	18.13
ATOM	1241	CD1	ILE A 172	26.426	43.320	80.163	1.00	13.83
ATOM	1242	N	LEU A 173	22.575	46.909	78.468	1.00	20.75

[Drawing 33]

ATOM	1243	CA	LEU	A	173	22.107	48.206	77.946	1.00	17.70
ATOM	1244	C	LEU	A	173	20.699	48.622	78.396	1.00	16.26
ATOM	1245	O	LEU	A	173	20.376	49.774	78.663	1.00	18.18
ATOM	1246	CB	LEU	A	173	22.176	48.201	76.419	1.00	16.81
ATOM	1247	CG	LEU	A	173	23.600	48.021	75.966	1.00	18.73
ATOM	1248	CD1	LEU	A	173	24.410	49.282	76.138	1.00	16.97
ATOM	1249	CD2	LEU	A	173	23.619	47.550	74.505	1.00	23.91
ATOM	1250	N	LYS	A	174	19.835	47.625	78.475	1.00	15.86
ATOM	1251	CA	LYS	A	174	18.494	47.970	78.945	1.00	19.21
ATOM	1252	C	LYS	A	174	18.453	48.415	80.429	1.00	21.86
ATOM	1253	O	LYS	A	174	17.800	49.404	80.737	1.00	20.00
ATOM	1254	CB	LYS	A	174	17.577	46.773	78.700	1.00	20.19
ATOM	1255	CG	LYS	A	174	16.094	47.130	78.731	1.00	27.84
ATOM	1256	CD	LYS	A	174	15.799	48.368	77.858	1.00	36.14
ATOM	1257	CE	LYS	A	174	14.309	48.628	77.774	1.00	40.56
ATOM	1258	NZ	LYS	A	174	13.775	48.622	79.156	1.00	49.45
ATOM	1259	N	ARG	A	175	19.250	47.698	81.286	1.00	21.93
ATOM	1260	CA	ARG	A	175	19.476	48.145	82.686	1.00	19.65
ATOM	1261	C	ARG	A	175	20.037	49.561	82.807	1.00	16.70
ATOM	1262	O	ARG	A	175	19.476	50.419	83.468	1.00	18.12
ATOM	1263	CB	ARG	A	175	20.345	47.126	83.467	1.00	21.25
ATOM	1264	CG	ARG	A	175	20.608	47.477	84.954	1.00	22.00
ATOM	1265	CD	ARG	A	175	19.259	47.669	85.656	1.00	25.63
ATOM	1266	NE	ARG	A	175	19.435	47.923	87.095	1.00	29.77
ATOM	1267	CZ	ARG	A	175	18.601	48.672	87.834	1.00	27.58
ATOM	1268	NH1	ARG	A	175	17.550	49.301	87.355	1.00	24.74
ATOM	1269	NH2	ARG	A	175	18.792	48.780	89.073	1.00	27.45
ATOM	1270	N	GLY	A	176	21.122	49.800	82.048	1.00	17.53
ATOM	1271	CA	GLY	A	176	21.698	51.143	81.893	1.00	17.18
ATOM	1272	C	GLY	A	176	20.679	52.214	81.552	1.00	21.18
ATOM	1273	O	GLY	A	176	20.582	53.278	82.149	1.00	21.85
ATOM	1274	N	TYR	A	177	19.847	51.887	80.547	1.00	22.48
ATOM	1275	CA	TYR	A	177	18.756	52.787	80.117	1.00	20.51
ATOM	1276	C	TYR	A	177	17.754	53.106	81.242	1.00	18.92
ATOM	1277	O	TYR	A	177	17.406	54.246	81.542	1.00	15.84
ATOM	1278	CB	TYR	A	177	18.007	52.120	78.939	1.00	23.76
ATOM	1279	CG	TYR	A	177	17.210	53.131	78.177	1.00	24.47
ATOM	1280	CD1	TYR	A	177	15.817	53.306	78.397	1.00	26.61
ATOM	1281	CD2	TYR	A	177	17.941	53.869	77.236	1.00	29.40
ATOM	1282	CE1	TYR	A	177	15.139	54.308	77.661	1.00	29.08
ATOM	1283	CE2	TYR	A	177	17.270	54.855	76.515	1.00	30.70
ATOM	1284	CZ	TYR	A	177	15.899	55.092	76.747	1.00	32.01
ATOM	1285	OH	TYR	A	177	15.401	56.167	76.020	1.00	41.52
ATOM	1286	N	GLU	A	178	17.354	52.008	81.867	1.00	19.45
ATOM	1287	CA	GLU	A	178	16.429	52.094	82.972	1.00	22.02
ATOM	1288	C	GLU	A	178	16.820	52.802	84.236	1.00	20.09
ATOM	1289	O	GLU	A	178	16.001	53.492	84.805	1.00	21.41
ATOM	1290	CB	GLU	A	178	16.010	50.731	83.357	1.00	25.45
ATOM	1291	CG	GLU	A	178	15.173	50.032	82.303	1.00	34.73
ATOM	1292	CD	GLU	A	178	13.893	50.810	81.951	1.00	40.36
ATOM	1293	OE1	GLU	A	178	13.432	51.667	82.707	1.00	33.51
ATOM	1294	OE2	GLU	A	178	13.352	50.556	80.876	1.00	45.77
ATOM	1295	N	LEU	A	179	18.090	52.695	84.609	1.00	19.63
ATOM	1296	CA	LEU	A	179	18.655	53.567	85.665	1.00	19.10

[Drawing 34]



ATOM	1297	C	LEU A 179	18.366	55.051	85.511	1.00	20.25
ATOM	1298	O	LEU A 179	17.838	55.726	86.374	1.00	19.26
ATOM	1299	CB	LEU A 179	20.178	53.361	85.813	1.00	17.45
ATOM	1300	CG	LEU A 179	20.610	52.013	86.426	1.00	18.23
ATOM	1301	CD1	LEU A 179	20.093	51.829	87.873	1.00	16.98
ATOM	1302	CD2	LEU A 179	22.124	51.811	86.340	1.00	16.34
ATOM	1303	N	GLY A 180	18.647	55.545	84.290	1.00	19.84
ATOM	1304	CA	GLY A 180	18.171	56.903	83.987	1.00	15.90
ATOM	1305	C	GLY A 180	16.655	57.072	84.027	1.00	17.05
ATOM	1306	O	GLY A 180	16.130	58.031	84.564	1.00	19.49
ATOM	1307	N	GLN A 181	15.923	56.068	83.478	1.00	18.19
ATOM	1308	CA	GLN A 181	14.448	56.207	83.522	1.00	17.92
ATOM	1309	C	GLN A 181	13.822	56.265	84.938	1.00	18.20
ATOM	1310	O	GLN A 181	12.903	57.008	85.258	1.00	19.66
ATOM	1311	CB	GLN A 181	13.716	55.189	82.620	1.00	15.39
ATOM	1312	CG	GLN A 181	13.936	55.324	81.073	1.00	15.18
ATOM	1313	CD	GLN A 181	13.823	56.763	80.634	1.00	13.30
ATOM	1314	OE1	GLN A 181	14.769	57.400	80.176	1.00	17.23
ATOM	1315	NE2	GLN A 181	12.626	57.300	80.812	1.00	12.82
ATOM	1316	N	SER A 182	14.440	55.497	85.821	1.00	20.03
ATOM	1317	CA	SER A 182	14.156	55.600	87.273	1.00	16.56
ATOM	1318	C	SER A 182	14.209	56.973	87.871	1.00	14.78
ATOM	1319	O	SER A 182	13.305	57.369	88.582	1.00	19.49
ATOM	1320	CB	SER A 182	15.056	54.630	88.021	1.00	15.31
ATOM	1321	OG	SER A 182	14.563	53.332	87.714	1.00	16.70
ATOM	1322	N	ARG A 183	15.246	57.738	87.523	1.00	16.99
ATOM	1323	CA	ARG A 183	15.289	59.169	87.858	1.00	15.54
ATOM	1324	C	ARG A 183	14.161	60.085	87.309	1.00	19.55
ATOM	1325	O	ARG A 183	13.693	61.039	87.956	1.00	17.04
ATOM	1326	CB	ARG A 183	16.661	59.785	87.569	1.00	14.08
ATOM	1327	CG	ARG A 183	17.811	59.024	88.265	1.00	19.49
ATOM	1328	CD	ARG A 183	17.716	59.007	89.816	1.00	21.46
ATOM	1329	NE	ARG A 183	18.519	57.930	90.434	1.00	22.16
ATOM	1330	C2	ARG A 183	19.509	58.121	91.300	1.00	19.15
ATOM	1331	NH1	ARG A 183	19.913	59.335	91.541	1.00	16.50
ATOM	1332	NH2	ARG A 183	20.042	57.081	91.914	1.00	18.34
ATOM	1333	N	VAL A 184	13.681	59.704	86.076	1.00	21.38
ATOM	1334	CA	VAL A 184	12.494	60.417	85.589	1.00	19.02
ATOM	1335	C	VAL A 184	11.194	60.051	86.301	1.00	16.98
ATOM	1336	O	VAL A 184	10.468	60.913	86.800	1.00	18.45
ATOM	1337	CB	VAL A 184	12.368	60.194	84.070	1.00	19.28
ATOM	1338	CG1	VAL A 184	11.057	60.717	83.486	1.00	17.84
ATOM	1339	CG2	VAL A 184	13.517	60.605	83.169	1.00	15.69
ATOM	1340	N	ILE A 185	10.977	58.734	86.408	1.00	17.32
ATOM	1341	CA	ILE A 185	9.834	58.241	87.202	1.00	21.14
ATOM	1342	C	ILE A 185	9.790	58.797	88.672	1.00	22.77
ATOM	1343	O	ILE A 185	8.749	59.230	89.142	1.00	22.95
ATOM	1344	CB	ILE A 185	9.810	56.695	87.193	1.00	20.65
ATOM	1345	CG1	ILE A 185	9.555	56.195	85.758	1.00	18.43
ATOM	1346	CG2	ILE A 185	8.776	56.133	88.202	1.00	18.29
ATOM	1347	CD1	ILE A 185	9.914	54.734	85.494	1.00	14.60
ATOM	1348	N	CYS A 186	10.976	58.837	89.332	1.00	20.34
ATOM	1349	CA	CYS A 186	11.005	59.262	90.745	1.00	21.26
ATOM	1350	C	CYS A 186	10.979	60.766	90.931	1.00	22.80

[Drawing 35]

ATOM	1351	O	CYS A 186	10.775	61.304	92.009	1.00	23.98
ATOM	1352	CB	CYS A 186	12.220	58.669	91.429	1.00	21.60
ATOM	1353	SG	CYS A 186	12.075	58.576	93.237	1.00	25.16
ATOM	1354	N	GLY A 187	11.149	61.494	89.814	1.00	20.34
ATOM	1355	CA	GLY A 187	11.023	62.949	89.981	1.00	13.75
ATOM	1356	C	GLY A 187	12.351	63.676	90.197	1.00	14.55
ATOM	1357	O	GLY A 187	12.436	64.871	90.453	1.00	16.08
ATOM	1358	N	TYR A 188	13.434	62.894	90.072	1.00	14.86
ATOM	1359	CA	TYR A 188	14.736	63.526	90.226	1.00	16.85
ATOM	1360	C	TYR A 188	15.214	64.366	89.046	1.00	20.24
ATOM	1361	O	TYR A 188	15.979	65.318	89.192	1.00	18.42
ATOM	1362	CB	TYR A 188	15.758	62.441	90.479	1.00	21.64
ATOM	1363	CG	TYR A 188	15.683	61.913	91.899	1.00	27.20
ATOM	1364	CD1	TYR A 188	16.748	62.226	92.737	1.00	32.00
ATOM	1365	CD2	TYR A 188	14.604	61.128	92.365	1.00	30.81
ATOM	1366	CE1	TYR A 188	16.727	61.784	94.071	1.00	35.38
ATOM	1367	CE2	TYR A 188	14.570	60.695	93.705	1.00	30.65
ATOM	1368	CZ	TYR A 188	15.624	61.071	94.556	1.00	35.88
ATOM	1369	OH	TYR A 188	15.607	60.787	95.912	1.00	41.39
ATOM	1370	N	HIS A 189	14.751	63.890	87.862	1.00	19.35
ATOM	1371	CA	HIS A 189	15.215	64.475	86.589	1.00	19.83
ATOM	1372	C	HIS A 189	14.108	64.550	85.551	1.00	16.85
ATOM	1373	O	HIS A 189	13.232	63.689	85.533	1.00	18.10
ATOM	1374	CB	HIS A 189	16.360	63.648	86.032	1.00	15.43
ATOM	1375	CG	HIS A 189	17.677	64.142	86.589	1.00	16.05
ATOM	1376	ND1	HIS A 189	18.154	65.384	86.414	1.00	17.24
ATOM	1377	CD2	HIS A 189	18.581	63.433	87.382	1.00	17.58
ATOM	1378	CE1	HIS A 189	19.347	65.503	87.080	1.00	16.38
ATOM	1379	NE2	HIS A 189	19.587	64.304	87.667	1.00	18.68
ATOM	1380	N	TRP A 190	14.183	65.611	84.723	1.00	18.99
ATOM	1381	CA	TRP A 190	13.341	65.719	83.490	1.00	17.22
ATOM	1382	C	TRP A 190	13.768	64.690	82.453	1.00	15.79
ATOM	1383	O	TRP A 190	14.942	64.354	82.416	1.00	15.77
ATOM	1384	CB	TRP A 190	13.502	67.102	82.855	1.00	16.12
ATOM	1385	CG	TRP A 190	13.134	68.178	83.857	1.00	12.39
ATOM	1386	CD1	TRP A 190	14.033	69.073	84.454	1.00	10.88
ATOM	1387	CD2	TRP A 190	11.800	68.581	84.295	1.00	14.35
ATOM	1388	NE1	TRP A 190	13.343	69.989	85.186	1.00	13.77
ATOM	1389	CE2	TRP A 190	11.976	69.731	85.141	1.00	10.71
ATOM	1390	CE3	TRP A 190	10.505	68.036	84.094	1.00	14.68
ATOM	1391	CZ2	TRP A 190	10.845	70.401	85.666	1.00	12.89
ATOM	1392	CZ3	TRP A 190	9.393	68.700	84.672	1.00	16.93
ATOM	1393	CH2	TRP A 190	9.557	69.875	85.441	1.00	12.82
ATOM	1394	N	GLN A 191	12.859	64.188	81.613	1.00	16.92
ATOM	1395	CA	GLN A 191	13.316	63.234	80.569	1.00	17.49
ATOM	1396	C	GLN A 191	14.519	63.720	79.696	1.00	15.64
ATOM	1397	O	GLN A 191	15.508	63.054	79.429	1.00	16.52
ATOM	1398	CB	GLN A 191	12.113	62.829	79.721	1.00	15.28
ATOM	1399	CG	GLN A 191	12.522	61.832	78.632	1.00	17.26
ATOM	1400	CD	GLN A 191	12.860	60.493	79.206	1.00	16.84
ATOM	1401	OE1	GLN A 191	12.086	59.920	79.946	1.00	21.21
ATOM	1402	NE2	GLN A 191	14.027	59.971	78.864	1.00	16.69
ATOM	1403	N	SER A 192	14.448	65.016	79.389	1.00	17.04
ATOM	1404	CA	SER A 192	15.564	65.622	78.666	1.00	15.81

[Drawing 36]

ATOM	1405	C	SER A 192	16.899	65.683	79.339	1.00	17.61
ATOM	1406	O	SER A 192	17.937	65.640	78.700	1.00	16.65
ATOM	1407	CB	SER A 192	15.209	67.005	78.211	1.00	15.87
ATOM	1408	OG	SER A 192	14.862	67.833	79.313	1.00	21.12
ATOM	1409	N	ASP A 193	16.886	65.712	80.681	1.00	17.44
ATOM	1410	CA	ASP A 193	18.190	65.648	81.360	1.00	15.23
ATOM	1411	C	ASP A 193	18.889	64.316	81.197	1.00	12.26
ATOM	1412	O	ASP A 193	20.113	64.204	81.054	1.00	14.16
ATOM	1413	CB	ASP A 193	18.036	65.832	82.887	1.00	16.01
ATOM	1414	CG	ASP A 193	17.367	67.116	83.311	1.00	14.57
ATOM	1415	OD1	ASP A 193	17.503	68.180	82.691	1.00	15.89
ATOM	1416	OD2	ASP A 193	16.673	67.038	84.312	1.00	19.14
ATOM	1417	N	VAL A 194	18.025	63.283	81.216	1.00	11.48
ATOM	1418	CA	VAL A 194	18.425	61.882	81.108	1.00	13.18
ATOM	1419	C	VAL A 194	18.851	61.478	79.663	1.00	15.63
ATOM	1420	O	VAL A 194	19.852	60.822	79.387	1.00	15.79
ATOM	1421	CB	VAL A 194	17.210	61.135	81.625	1.00	16.33
ATOM	1422	CG1	VAL A 194	17.152	61.202	83.184	1.00	19.26
ATOM	1423	CG2	VAL A 194	17.079	59.712	81.106	1.00	17.70
ATOM	1424	N	ASP A 195	18.050	61.992	78.728	1.00	16.54
ATOM	1425	CA	ASP A 195	18.488	61.921	77.332	1.00	16.55
ATOM	1426	C	ASP A 195	19.801	62.636	77.029	1.00	14.74
ATOM	1427	O	ASP A 195	20.758	62.076	76.519	1.00	18.92
ATOM	1428	CB	ASP A 195	17.367	62.455	76.477	1.00	15.91
ATOM	1429	CG	ASP A 195	16.139	61.563	76.560	1.00	19.86
ATOM	1430	OD1	ASP A 195	16.153	60.385	76.922	1.00	27.62
ATOM	1431	OD2	ASP A 195	15.090	62.069	76.264	1.00	26.20
ATOM	1432	N	ALA A 196	19.902	63.900	77.450	1.00	15.85
ATOM	1433	CA	ALA A 196	21.203	64.555	77.312	1.00	14.73
ATOM	1434	C	ALA A 196	22.383	63.806	77.932	1.00	18.85
ATOM	1435	O	ALA A 196	23.512	63.751	77.429	1.00	21.06
ATOM	1436	CB	ALA A 196	21.134	65.950	77.904	1.00	13.59
ATOM	1437	N	ALA A 197	22.056	63.177	79.091	1.00	19.14
ATOM	1438	CA	ALA A 197	23.098	62.442	79.808	1.00	17.62
ATOM	1439	C	ALA A 197	23.644	61.202	79.090	1.00	17.71
ATOM	1440	O	ALA A 197	24.851	60.931	79.104	1.00	18.18
ATOM	1441	CB	ALA A 197	22.587	62.002	81.181	1.00	15.91
ATOM	1442	N	ARG A 198	22.711	60.477	78.418	1.00	16.04
ATOM	1443	CA	ARG A 198	23.238	59.409	77.565	1.00	15.41
ATOM	1444	C	ARG A 198	24.179	59.843	76.413	1.00	14.99
ATOM	1445	O	ARG A 198	25.194	59.219	76.113	1.00	17.07
ATOM	1446	CB	ARG A 198	22.136	58.469	77.080	1.00	14.50
ATOM	1447	CG	ARG A 198	21.195	58.043	78.179	1.00	16.67
ATOM	1448	CD	ARG A 198	20.142	57.044	77.730	1.00	19.20
ATOM	1449	NE	ARG A 198	19.280	56.629	78.849	1.00	22.72
ATOM	1450	CZ	ARG A 198	18.003	57.012	79.061	1.00	22.30
ATOM	1451	NH1	ARG A 198	17.412	57.905	78.325	1.00	20.95
ATOM	1452	NH2	ARG A 198	17.292	56.518	80.045	1.00	21.57
ATOM	1453	N	VAL A 199	23.907	61.030	75.842	1.00	17.69
ATOM	1454	CA	VAL A 199	24.961	61.510	74.913	1.00	17.44
ATOM	1455	C	VAL A 199	26.376	61.736	75.457	1.00	18.48
ATOM	1456	O	VAL A 199	27.360	61.145	74.988	1.00	19.25
ATOM	1457	CB	VAL A 199	24.452	62.820	74.284	1.00	15.93
ATOM	1458	CG1	VAL A 199	25.350	63.540	73.279	1.00	11.45

[Drawing 37]

ATOM	1459	CG2	VAL	A	199	23.072	62.640	73.680	1.00	15.33
ATOM	1460	N	VAL	A	200	26.471	62.548	76.550	1.00	18.52
ATOM	1461	CA	VAL	A	200	27.822	62.723	77.153	1.00	16.27
ATOM	1462	C	VAL	A	200	28.442	61.461	77.794	1.00	14.37
ATOM	1463	O	VAL	A	200	29.643	61.247	77.797	1.00	17.25
ATOM	1464	CB	VAL	A	200	27.811	63.938	78.100	1.00	16.56
ATOM	1465	CG1	VAL	A	200	26.761	63.894	79.246	1.00	13.52
ATOM	1466	CG2	VAL	A	200	27.666	65.177	77.226	1.00	17.14
ATOM	1467	N	GLY	A	201	27.556	60.570	78.283	1.00	14.98
ATOM	1468	CA	GLY	A	201	27.998	59.297	78.836	1.00	13.20
ATOM	1469	C	GLY	A	201	28.609	58.377	77.824	1.00	16.81
ATOM	1470	O	GLY	A	201	29.588	57.701	78.067	1.00	17.03
ATOM	1471	N	SER	A	202	28.034	58.413	76.614	1.00	17.82
ATOM	1472	CA	SER	A	202	28.757	57.750	75.509	1.00	16.70
ATOM	1473	C	SER	A	202	30.087	58.390	75.104	1.00	13.91
ATOM	1474	O	SER	A	202	31.117	57.765	74.939	1.00	18.47
ATOM	1475	CB	SER	A	202	27.813	57.511	74.303	1.00	15.94
ATOM	1476	OG	SER	A	202	27.634	58.737	73.600	1.00	19.26
ATOM	1477	N	ALA	A	203	30.094	59.719	75.030	1.00	14.76
ATOM	1478	CA	ALA	A	203	31.333	60.383	74.641	1.00	14.41
ATOM	1479	C	ALA	A	203	32.527	60.110	75.563	1.00	17.92
ATOM	1480	O	ALA	A	203	33.652	59.803	75.177	1.00	16.36
ATOM	1481	CB	ALA	A	203	31.042	61.872	74.572	1.00	13.61
ATOM	1482	N	VAL	A	204	32.200	60.126	76.880	1.00	18.27
ATOM	1483	CA	VAL	A	204	33.290	59.835	77.823	1.00	16.45
ATOM	1484	C	VAL	A	204	33.834	58.394	77.718	1.00	13.88
ATOM	1485	O	VAL	A	204	35.015	58.177	77.916	1.00	17.64
ATOM	1486	CB	VAL	A	204	32.893	60.245	79.285	1.00	16.63
ATOM	1487	CG1	VAL	A	204	34.131	60.323	80.177	1.00	16.51
ATOM	1488	CG2	VAL	A	204	31.836	59.301	79.862	1.00	13.53
ATOM	1489	N	VAL	A	205	32.971	57.392	77.355	1.00	15.31
ATOM	1490	CA	VAL	A	205	33.648	56.100	77.152	1.00	17.30
ATOM	1491	C	VAL	A	205	34.636	56.018	75.953	1.00	19.20
ATOM	1492	O	VAL	A	205	35.644	55.311	76.002	1.00	19.08
ATOM	1493	CB	VAL	A	205	32.563	55.014	77.035	1.00	19.10
ATOM	1494	CG1	VAL	A	205	32.812	53.549	76.681	1.00	16.51
ATOM	1495	CG2	VAL	A	205	31.797	55.088	78.343	1.00	17.27
ATOM	1496	N	ALA	A	206	34.409	56.893	74.934	1.00	21.03
ATOM	1497	CA	ALA	A	206	35.452	57.018	73.888	1.00	19.17
ATOM	1498	C	ALA	A	206	36.765	57.498	74.469	1.00	19.27
ATOM	1499	O	ALA	A	206	37.809	56.868	74.353	1.00	18.59
ATOM	1500	CB	ALA	A	206	34.982	57.988	72.809	1.00	16.60
ATOM	1501	N	THR	A	207	36.643	58.597	75.234	1.00	20.20
ATOM	1502	CA	THR	A	207	37.873	59.078	75.903	1.00	20.52
ATOM	1503	C	THR	A	207	38.613	58.126	76.838	1.00	21.84
ATOM	1504	O	THR	A	207	39.831	58.030	76.898	1.00	23.45
ATOM	1505	CB	THR	A	207	37.659	60.341	76.674	1.00	19.84
ATOM	1506	OG1	THR	A	207	36.577	61.100	76.137	1.00	20.11
ATOM	1507	CG2	THR	A	207	38.945	61.141	76.710	1.00	21.15
ATOM	1508	N	LEU	A	208	37.806	57.345	77.574	1.00	23.89
ATOM	1509	CA	LEU	A	208	38.323	56.332	78.510	1.00	22.19
ATOM	1510	C	LEU	A	208	39.165	55.285	77.783	1.00	25.28
ATOM	1511	O	LEU	A	208	40.232	54.880	78.228	1.00	24.41
ATOM	1512	CB	LEU	A	208	37.170	55.700	79.312	1.00	21.93

[Drawing 38]

ATOM	1513	CG	LEU A 208	36.238	56.370	80.325	1.00	24.99
ATOM	1514	CD1	LEU A 208	35.117	55.631	81.058	1.00	26.55
ATOM	1515	CD2	LEU A 208	37.303	56.685	81.377	1.00	22.67
ATOM	1516	N	HIS A 209	38.666	54.873	76.588	1.00	24.64
ATOM	1517	CA	HIS A 209	39.495	53.970	75.766	1.00	20.81
ATOM	1518	C	HIS A 209	40.863	54.530	75.277	1.00	19.15
ATOM	1519	O	HIS A 209	41.807	53.872	74.934	1.00	20.30
ATOM	1520	CB	HIS A 209	38.656	53.449	74.595	1.00	16.87
ATOM	1521	CG	HIS A 209	37.588	52.476	74.994	1.00	13.42
ATOM	1522	ND1	HIS A 209	36.335	52.782	75.375	1.00	14.12
ATOM	1523	CD2	HIS A 209	37.686	51.099	74.975	1.00	12.37
ATOM	1524	CE1	HIS A 209	35.653	51.616	75.586	1.00	10.36
ATOM	1525	NE2	HIS A 209	36.493	50.590	75.334	1.00	13.53
ATOM	1526	N	THR A 210	41.035	55.827	75.336	1.00	20.82
ATOM	1527	CA	THR A 210	42.393	56.384	75.116	1.00	21.40
ATOM	1528	C	THR A 210	43.396	56.387	76.298	1.00	26.34
ATOM	1529	O	THR A 210	44.567	56.745	76.188	1.00	27.83
ATOM	1530	CB	THR A 210	42.315	57.836	74.662	1.00	22.02
ATOM	1531	OG1	THR A 210	42.096	58.723	75.795	1.00	25.04
ATOM	1532	CG2	THR A 210	41.307	58.070	73.528	1.00	20.46
ATOM	1533	N	ASN A 211	42.844	56.032	77.482	1.00	26.32
ATOM	1534	CA	ASN A 211	43.544	56.135	78.782	1.00	23.64
ATOM	1535	C	ASN A 211	44.212	54.824	79.204	1.00	20.62
ATOM	1536	O	ASN A 211	43.591	53.785	79.374	1.00	22.28
ATOM	1537	CB	ASN A 211	42.563	56.749	79.827	1.00	24.99
ATOM	1538	CG	ASN A 211	43.226	56.863	81.206	1.00	24.09
ATOM	1539	OD1	ASN A 211	43.320	55.886	81.935	1.00	25.25
ATOM	1540	ND2	ASN A 211	43.689	58.038	81.566	1.00	21.24
ATOM	1541	N	PRO A 212	45.563	54.884	79.353	1.00	22.01
ATOM	1542	CA	PRO A 212	46.337	53.660	79.633	1.00	21.52
ATOM	1543	C	PRO A 212	45.859	52.883	80.848	1.00	22.52
ATOM	1544	O	PRO A 212	45.670	51.673	80.882	1.00	22.12
ATOM	1545	CB	PRO A 212	47.743	54.190	79.845	1.00	22.52
ATOM	1546	CG	PRO A 212	47.805	55.535	79.117	1.00	25.40
ATOM	1547	CD	PRO A 212	46.391	56.076	79.175	1.00	22.01
ATOM	1548	N	ALA A 213	45.626	53.674	81.897	1.00	23.96
ATOM	1549	CA	ALA A 213	45.139	53.025	83.140	1.00	23.57
ATOM	1550	C	ALA A 213	43.797	52.337	83.019	1.00	21.76
ATOM	1551	O	ALA A 213	43.600	51.185	83.403	1.00	24.96
ATOM	1552	CB	ALA A 213	45.039	54.071	84.259	1.00	21.55
ATOM	1553	N	PHE A 214	42.885	53.085	82.373	1.00	19.30
ATOM	1554	CA	PHE A 214	41.617	52.431	82.017	1.00	20.02
ATOM	1555	C	PHE A 214	41.798	51.170	81.197	1.00	20.38
ATOM	1556	O	PHE A 214	41.255	50.120	81.510	1.00	18.82
ATOM	1557	CB	PHE A 214	40.690	53.445	81.314	1.00	23.58
ATOM	1558	CG	PHE A 214	39.367	52.839	80.840	1.00	26.35
ATOM	1559	CD1	PHE A 214	38.249	52.765	81.711	1.00	24.66
ATOM	1560	CD2	PHE A 214	39.262	52.365	79.507	1.00	23.08
ATOM	1561	CE1	PHE A 214	37.032	52.191	81.265	1.00	27.05
ATOM	1562	CE2	PHE A 214	38.052	51.792	79.077	1.00	19.74
ATOM	1563	CZ	PHE A 214	36.951	51.697	79.944	1.00	22.04
ATOM	1564	N	GLN A 215	42.654	51.298	80.149	1.00	22.02
ATOM	1565	CA	GLN A 215	42.904	50.137	79.275	1.00	21.33
ATOM	1566	C	GLN A 215	43.354	48.889	79.995	1.00	21.73

[Drawing 30]

ATOM	1567	O	GLN A 215	42.823	47.783	79.875	1.00	21.17
ATOM	1568	CB	GLN A 215	43.970	50.520	78.278	1.00	22.37
ATOM	1569	CG	GLN A 215	43.483	51.517	77.261	1.00	22.30
ATOM	1570	CD	GLN A 215	44.662	52.026	76.479	1.00	28.18
ATOM	1571	OE1	GLN A 215	45.821	51.695	76.664	1.00	32.27
ATOM	1572	NE2	GLN A 215	44.359	52.947	75.605	1.00	28.35
ATOM	1573	N	GLN A 216	44.375	49.154	80.845	1.00	24.60
ATOM	1574	CA	GLN A 216	44.876	48.089	81.718	1.00	25.81
ATOM	1575	C	GLN A 216	43.909	47.530	82.715	1.00	23.07
ATOM	1576	O	GLN A 216	43.822	46.328	82.899	1.00	22.91
ATOM	1577	CB	GLN A 216	46.052	48.544	82.517	1.00	33.78
ATOM	1578	CG	GLN A 216	47.181	49.037	81.631	1.00	49.94
ATOM	1579	CD	GLN A 216	48.161	49.693	82.574	1.00	61.57
ATOM	1580	OE1	GLN A 216	48.354	49.243	83.704	1.00	69.34
ATOM	1581	NE2	GLN A 216	48.737	50.805	82.114	1.00	63.50
ATOM	1582	N	GLN A 217	43.155	48.439	83.377	1.00	22.58
ATOM	1583	CA	GLN A 217	42.099	47.917	84.261	1.00	23.69
ATOM	1584	C	GLN A 217	40.971	47.113	83.590	1.00	24.92
ATOM	1585	O	GLN A 217	40.480	46.102	84.088	1.00	24.09
ATOM	1586	CB	GLN A 217	41.565	49.042	85.189	1.00	23.44
ATOM	1587	CG	GLN A 217	40.720	48.541	86.407	1.00	23.24
ATOM	1588	CD	GLN A 217	41.489	47.589	87.335	1.00	21.58
ATOM	1589	OE1	GLN A 217	42.676	47.749	87.598	1.00	24.82
ATOM	1590	NE2	GLN A 217	40.827	46.516	87.744	1.00	19.85
ATOM	1591	N	LEU A 218	40.628	47.595	82.390	1.00	26.00
ATOM	1592	CA	LEU A 218	39.701	46.859	81.532	1.00	23.47
ATOM	1593	C	LEU A 218	40.195	45.495	81.093	1.00	21.96
ATOM	1594	O	LEU A 218	39.476	44.515	81.209	1.00	22.51
ATOM	1595	CB	LEU A 218	39.309	47.724	80.327	1.00	23.65
ATOM	1596	CG	LEU A 218	38.292	47.073	79.369	1.00	21.04
ATOM	1597	CD1	LEU A 218	38.103	47.980	78.168	1.00	25.30
ATOM	1598	CD2	LEU A 218	36.952	46.736	80.004	1.00	13.22
ATOM	1599	N	GLN A 219	41.451	45.425	80.640	1.00	23.49
ATOM	1600	CA	GLN A 219	42.033	44.079	80.457	1.00	29.37
ATOM	1601	C	GLN A 219	41.880	43.156	81.681	1.00	29.60
ATOM	1602	O	GLN A 219	41.455	42.016	81.569	1.00	29.63
ATOM	1603	CB	GLN A 219	43.544	44.131	80.199	1.00	37.46
ATOM	1604	CG	GLN A 219	44.052	44.703	78.867	1.00	51.74
ATOM	1605	CD	GLN A 219	45.511	45.267	78.911	1.00	60.29
ATOM	1606	OE1	GLN A 219	46.415	44.774	79.568	1.00	65.45
ATOM	1607	NE2	GLN A 219	45.764	46.352	78.161	1.00	60.81
ATOM	1608	N	LYS A 220	42.206	43.722	82.879	1.00	28.28
ATOM	1609	CA	LYS A 220	42.004	42.926	84.111	1.00	26.68
ATOM	1610	C	LYS A 220	40.588	42.446	84.386	1.00	24.54
ATOM	1611	O	LYS A 220	40.347	41.275	84.640	1.00	26.87
ATOM	1612	CB	LYS A 220	42.591	43.631	85.319	1.00	29.93
ATOM	1613	CG	LYS A 220	44.019	43.952	84.934	1.00	36.96
ATOM	1614	CD	LYS A 220	45.015	44.044	86.081	1.00	47.54
ATOM	1615	CE	LYS A 220	44.741	45.121	87.121	1.00	55.28
ATOM	1616	NZ	LYS A 220	44.868	46.456	86.510	1.00	61.92
ATOM	1617	N	ALA A 221	39.630	43.379	84.217	1.00	21.04
ATOM	1618	CA	ALA A 221	38.215	42.960	84.307	1.00	18.69
ATOM	1619	C	ALA A 221	37.761	41.903	83.291	1.00	24.31
ATOM	1620	O	ALA A 221	37.095	40.921	83.598	1.00	26.78

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ATOM	1621	CB	ALA	A	221	37.306	44.177	84.140	1.00	14.85
ATOM	1622	N	LYS	A	222	38.223	42.106	82.029	1.00	24.15
ATOM	1623	CA	LYS	A	222	38.065	41.018	81.046	1.00	23.96
ATOM	1624	C	LYS	A	222	38.668	39.675	81.431	1.00	22.61
ATOM	1625	O	LYS	A	222	38.023	38.628	81.422	1.00	21.88
ATOM	1626	CB	LYS	A	222	38.591	41.444	79.659	1.00	22.92
ATOM	1627	CG	LYS	A	222	37.682	42.516	79.109	1.00	22.76
ATOM	1628	CD	LYS	A	222	38.038	42.903	77.691	1.00	22.50
ATOM	1629	CE	LYS	A	222	37.050	43.918	77.109	1.00	22.07
ATOM	1630	NZ	LYS	A	222	37.556	44.613	75.909	1.00	21.47
ATOM	1631	N	ALA	A	223	39.949	39.728	81.830	1.00	22.84
ATOM	1632	CA	ALA	A	223	40.533	38.472	82.353	1.00	25.17
ATOM	1633	C	ALA	A	223	39.812	37.842	83.543	1.00	26.19
ATOM	1634	O	ALA	A	223	39.534	36.652	83.573	1.00	27.99
ATOM	1635	CB	ALA	A	223	42.013	38.638	82.691	1.00	21.36
ATOM	1636	N	GLU	A	224	39.424	38.696	84.487	1.00	27.72
ATOM	1637	CA	GLU	A	224	38.643	38.187	85.610	1.00	27.59
ATOM	1638	C	GLU	A	224	37.338	37.525	85.191	1.00	28.89
ATOM	1639	O	GLU	A	224	36.971	36.412	85.568	1.00	28.75
ATOM	1640	CB	GLU	A	224	38.476	39.348	86.606	1.00	29.18
ATOM	1641	CG	GLU	A	224	37.470	39.099	87.741	1.00	29.05
ATOM	1642	CD	GLU	A	224	37.335	40.348	88.557	1.00	29.41
ATOM	1643	OE1	GLU	A	224	36.506	41.189	88.269	1.00	28.08
ATOM	1644	OE2	GLU	A	224	38.060	40.487	89.516	1.00	31.14
ATOM	1645	N	PHE	A	225	36.659	38.233	84.288	1.00	29.33
ATOM	1646	CA	PHE	A	225	35.398	37.699	83.770	1.00	28.70
ATOM	1647	C	PHE	A	225	35.551	36.354	83.061	1.00	31.53
ATOM	1648	O	PHE	A	225	34.802	35.399	83.222	1.00	29.17
ATOM	1649	CB	PHE	A	225	34.786	38.756	82.858	1.00	26.48
ATOM	1650	CG	PHE	A	225	33.449	38.281	82.361	1.00	25.90
ATOM	1651	CD1	PHE	A	225	32.361	38.258	83.250	1.00	28.71
ATOM	1652	CD2	PHE	A	225	33.317	37.854	81.022	1.00	28.64
ATOM	1653	CE1	PHE	A	225	31.129	37.758	82.817	1.00	29.98
ATOM	1654	CE2	PHE	A	225	32.074	37.365	80.564	1.00	28.53
ATOM	1655	CZ	PHE	A	225	30.998	37.309	81.479	1.00	30.02
ATOM	1656	N	ALA	A	226	36.635	36.308	82.289	1.00	31.91
ATOM	1657	CA	ALA	A	226	36.996	35.055	81.643	1.00	36.17
ATOM	1658	C	ALA	A	226	37.178	33.829	82.536	1.00	40.94
ATOM	1659	O	ALA	A	226	36.704	32.735	82.271	1.00	41.75
ATOM	1660	CB	ALA	A	226	38.284	35.261	80.877	1.00	33.81
ATOM	1661	N	GLN	A	227	37.883	34.081	83.647	1.00	44.91
ATOM	1662	CA	GLN	A	227	38.067	32.931	84.543	1.00	49.32
ATOM	1663	C	GLN	A	227	36.782	32.579	85.233	1.00	51.62
ATOM	1664	O	GLN	A	227	36.396	31.467	85.528	1.00	50.02
ATOM	1665	CB	GLN	A	227	39.239	33.150	85.499	1.00	50.80
ATOM	1666	CG	GLN	A	227	40.441	33.937	84.900	1.00	59.92
ATOM	1667	CD	GLN	A	227	40.812	33.681	83.397	1.00	68.68
ATOM	1668	OE1	GLN	A	227	40.799	32.592	82.834	1.00	73.97
ATOM	1669	NE2	GLN	A	227	41.221	34.764	82.726	1.00	65.71
ATOM	1670	N	HIS	A	228	36.041	33.669	85.411	1.00	58.91
ATOM	1671	CA	HIS	A	228	34.687	33.501	85.925	1.00	65.53
ATOM	1672	C	HIS	A	228	33.816	32.519	85.143	1.00	68.04
ATOM	1673	O	HIS	A	228	33.014	31.764	85.662	1.00	67.46
ATOM	1674	CB	HIS	A	228	34.091	34.903	86.045	1.00	68.11

[Drawing 41]

ATOM	1675	CG	HIS A 228	32.632	34.780	86.283	1.00	71.87
ATOM	1676	ND1	HIS A 228	31.729	34.968	85.313	1.00	74.51
ATOM	1677	CD2	HIS A 228	32.007	34.363	87.458	1.00	75.53
ATOM	1678	CE1	HIS A 228	30.511	34.660	85.852	1.00	78.68
ATOM	1679	NE2	HIS A 228	30.682	34.288	87.171	1.00	80.02
ATOM	1680	N	GLN A 229	34.061	32.545	83.846	1.00	74.45
ATOM	1681	CA	GLN A 229	33.306	31.659	82.963	1.00	81.06
ATOM	1682	C	GLN A 229	33.569	30.149	83.028	1.00	85.59
ATOM	1683	O	GLN A 229	33.123	29.427	82.135	1.00	86.52
ATOM	1684	CB	GLN A 229	33.477	32.181	81.530	1.00	81.47
ATOM	1685	CG	GLN A 229	33.002	33.631	81.335	1.00	81.55
ATOM	1686	CD	GLN A 229	31.488	33.690	81.352	1.00	83.81
ATOM	1687	OE1	GLN A 229	30.804	33.832	82.355	1.00	82.35
ATOM	1688	NE2	GLN A 229	30.950	33.588	80.141	1.00	86.80
ATOM	1689	N	LYS A 230	34.317	29.749	84.086	1.00	91.08
ATOM	1690	CA	LYS A 230	34.965	28.444	84.325	1.00	95.45
ATOM	1691	CB	LYS A 230	33.976	27.245	84.052	1.00	97.51
ATOM	1692	CG	LYS A 230	34.256	26.053	83.073	1.00	98.30
ATOM	1693	CD	LYS A 230	34.035	26.121	81.534	1.00	98.30
ATOM	1694	CE	LYS A 230	34.810	27.172	80.713	1.00	100.00
ATOM	1695	NZ	LYS A 230	36.244	27.239	81.067	1.00	100.00
ATOM	1696	C	LYS A 230	36.409	28.279	83.743	1.00	97.06
ATOM	1697	OCT1	LYS A 230	36.876	29.108	82.942	1.00	95.86
ATOM	1698	OCT2	LYS A 230	37.052	27.241	83.957	1.00	99.89
ATOM	1935	S	SO4 S 231	22.561	63.872	89.148	1.00	45.29
ATOM	1936	O1	SO4 S 231	21.748	62.858	88.279	1.00	50.45
ATOM	1937	O2	SO4 S 231	21.648	64.707	90.036	1.00	51.74
ATOM	1938	O3	SO4 S 231	23.551	63.095	90.035	1.00	49.75
ATOM	1939	O4	SO4 S 231	23.260	64.912	88.285	1.00	44.08
ATOM	1	O	HOH W 232	10.522	63.513	85.670	1.00	17.86
ATOM	2	O	HOH W 233	34.116	63.633	80.578	1.00	20.45
ATOM	3	O	HOH W 234	7.928	61.775	88.229	1.00	15.62
ATOM	4	O	HOH W 235	10.374	64.545	82.597	1.00	14.58
ATOM	5	O	HOH W 236	15.375	75.641	85.508	1.00	22.07
ATOM	6	O	HOH W 237	20.773	44.507	86.785	1.00	18.67
ATOM	7	O	HOH W 238	32.701	49.912	75.935	1.00	15.79
ATOM	8	O	HOH W 239	21.979	72.096	84.493	1.00	19.08
ATOM	9	O	HOH W 240	13.158	73.905	82.705	1.00	27.34
ATOM	10	O	HOH W 241	14.358	71.880	73.410	1.00	26.83
ATOM	11	O	HOH W 242	5.537	80.043	74.802	1.00	23.33
ATOM	12	O	HOH W 243	36.136	62.604	78.407	1.00	23.19
ATOM	13	O	HOH W 244	30.393	53.028	87.579	1.00	19.02
ATOM	14	O	HOH W 245	28.532	49.107	93.252	1.00	21.32
ATOM	15	O	HOH W 246	24.657	73.146	75.882	1.00	20.92
ATOM	16	O	HOH W 247	10.080	55.567	81.848	1.00	33.80
ATOM	17	O	HOH W 248	29.907	52.840	73.379	1.00	22.59
ATOM	18	O	HOH W 249	38.583	48.054	74.575	1.00	24.10
ATOM	19	O	HOH W 250	29.465	68.020	86.676	1.00	32.30
ATOM	20	O	HOH W 251	12.847	73.680	85.460	1.00	40.76
ATOM	21	O	HOH W 252	5.516	59.770	95.129	1.00	40.84
ATOM	22	O	HOH W 253	42.504	47.354	77.319	1.00	30.77
ATOM	23	O	HOH W 254	13.495	75.378	74.412	1.00	22.57
ATOM	24	O	HOH W 255	17.100	76.564	77.737	1.00	30.00
ATOM	25	O	HOH W 256	33.508	40.103	102.712	1.00	26.49

[Drawing 42]



ATOM	26	O	HOH W 257	20.825	55.648	81.278	1.00	20.11
ATOM	27	O	HOH W 258	19.730	61.701	89.970	1.00	23.10
ATOM	28	O	HOH W 259	4.363	74.520	80.720	1.00	33.74
ATOM	29	O	HOH W 260	31.490	42.656	98.480	1.00	34.19
ATOM	30	O	HOH W 261	6.696	75.130	78.477	1.00	15.66
ATOM	31	O	HOH W 262	10.667	67.023	75.103	1.00	38.86
ATOM	32	O	HOH W 263	8.252	64.433	92.307	1.00	23.15
ATOM	33	O	HOH W 264	41.924	51.223	74.247	1.00	30.19
ATOM	34	O	HOH W 265	1.437	67.705	89.398	1.00	39.48
ATOM	35	O	HOH W 266	4.055	66.946	91.467	1.00	29.22
ATOM	36	O	HOH W 267	3.092	69.112	84.950	1.00	25.58
ATOM	37	O	HOH W 268	9.537	59.065	79.795	1.00	30.90
ATOM	38	O	HOH W 269	9.306	83.197	79.638	1.00	44.19
ATOM	39	O	HOH W 270	34.786	41.166	75.522	1.00	32.98
ATOM	40	O	HOH W 271	28.084	37.193	84.163	1.00	30.43
ATOM	41	O	HOH W 272	40.742	49.227	76.024	1.00	21.82
ATOM	42	O	HOH W 273	35.074	40.712	85.668	1.00	29.87
ATOM	43	O	HOH W 274	30.318	45.526	96.384	1.00	35.57
ATOM	44	O	HOH W 275	31.493	69.162	80.850	1.00	19.51
ATOM	45	O	HOH W 276	42.914	61.700	76.016	1.00	28.69
ATOM	46	O	HOH W 277	34.422	64.714	92.625	1.00	38.81
ATOM	47	O	HOH W 278	13.405	78.374	80.916	1.00	25.22
ATOM	48	O	HOH W 279	44.634	57.811	84.433	1.00	31.73
ATOM	49	O	HOH W 280	44.303	60.992	82.740	1.00	28.14
ATOM	50	O	HOH W 281	32.596	51.432	73.247	1.00	22.63
ATOM	51	O	HOH W 282	22.182	40.126	75.125	1.00	27.50
ATOM	52	O	HOH W 283	18.482	55.362	89.100	1.00	21.25
ATOM	53	O	HOH W 284	36.960	42.360	74.192	1.00	28.88
ATOM	54	O	HOH W 285	35.881	48.845	94.047	1.00	26.90
ATOM	55	O	HOH W 286	26.212	59.698	94.760	1.00	23.37
ATOM	56	O	HOH W 287	29.246	44.303	73.369	1.00	40.38
ATOM	57	O	HOH W 288	27.356	35.947	80.422	1.00	31.74
ATOM	58	O	HOH W 289	40.482	45.029	76.766	1.00	30.88
ATOM	59	O	HOH W 290	24.864	58.724	91.112	1.00	25.30
ATOM	60	O	HOH W 291	28.560	61.547	91.755	1.00	39.37
ATOM	61	O	HOH W 292	27.888	63.113	90.252	1.00	40.28
ATOM	62	O	HOH W 293	31.069	41.023	103.435	1.00	38.13
ATOM	63	O	HOH W 294	5.144	47.860	86.978	1.00	37.63
ATOM	64	O	HOH W 295	29.373	52.425	90.409	1.00	21.69
ATOM	65	O	HOH W 296	41.571	51.401	87.864	1.00	31.72
ATOM	66	O	HOH W 297	35.633	56.807	101.396	1.00	42.27
ATOM	67	O	HOH W 298	35.257	40.157	78.063	1.00	30.17
ATOM	68	O	HOH W 299	33.734	71.189	79.910	1.00	32.64
ATOM	69	O	HOH W 300	17.659	69.593	75.158	1.00	46.73
ATOM	70	O	HOH W 301	17.005	72.932	72.774	1.00	33.93
ATOM	71	O	HOH W 302	15.769	48.059	85.107	1.00	24.21
ATOM	72	O	HOH W 303	15.023	64.697	75.333	1.00	39.99
ATOM	73	O	HOH W 304	13.546	67.305	74.469	1.00	38.11
ATOM	74	O	HOH W 305	30.044	75.863	82.738	1.00	29.02
ATOM	75	O	HOH W 306	5.253	66.383	98.323	1.00	61.09
ATOM	76	O	HOH W 307	25.914	72.829	89.073	1.00	48.08
ATOM	77	O	HOH W 308	38.474	67.620	76.050	1.00	32.88
ATOM	78	O	HOH W 309	34.101	41.534	100.215	1.00	39.54
ATOM	79	O	HOH W 310	29.974	37.419	76.650	1.00	39.99

[Drawing 43]

ATOM	80	O	HOH W 311	17.829	44.406	81.773	1.00	29.29
ATOM	81	O	HOH W 312	17.766	66.478	75.705	1.00	34.51
ATOM	82	O	HOH W 313	35.983	70.225	78.152	1.00	38.85
ATOM	83	O	HOH W 314	18.063	58.644	75.592	1.00	33.24
ATOM	84	O	HOH W 315	17.740	45.824	75.692	1.00	31.29
ATOM	85	O	HOH W 316	21.442	55.668	101.498	1.00	30.06
ATOM	86	O	HOH W 317	30.660	37.639	105.501	1.00	46.34
ATOM	87	O	HOH W 318	28.143	47.582	99.410	1.00	71.00
ATOM	88	O	HOH W 319	11.398	65.394	76.821	1.00	34.86
ATOM	89	O	HOH W 320	31.737	45.760	98.744	1.00	38.11
ATOM	90	O	HOH W 321	16.084	45.559	87.137	1.00	43.68
ATOM	91	O	HOH W 322	36.498	37.962	78.989	1.00	35.45
ATOM	92	O	HOH W 323	41.868	42.172	76.980	1.00	56.04
ATOM	93	O	HOH W 324	44.704	68.004	76.606	1.00	73.28
ATOM	94	O	HOH W 325	30.214	44.935	101.119	1.00	28.63
ATOM	95	O	HOH W 326	43.719	69.244	83.004	1.00	32.20
ATOM	96	O	HOH W 327	7.992	54.768	93.490	1.00	36.05
ATOM	97	O	HOH W 328	11.059	49.604	75.476	1.00	43.80
ATOM	98	O	HOH W 329	17.730	37.202	79.516	1.00	44.41
ATOM	99	O	HOH W 330	14.170	59.796	74.913	1.00	70.26
ATOM	100	O	HOH W 331	28.648	70.326	88.645	1.00	34.35
ATOM	101	O	HOH W 332	16.146	57.197	73.492	1.00	49.27
ATOM	102	O	HOH W 333	11.086	52.502	82.116	1.00	39.47
ATOM	103	O	HOH W 334	15.950	60.744	73.392	1.00	63.16
ATOM	104	O	HOH W 335	23.809	74.443	89.142	1.00	63.73
ATOM	105	O	HOH W 336	43.077	70.945	86.543	1.00	41.77
ATOM	106	O	HOH W 337	44.625	68.578	85.466	1.00	42.53
ATOM	107	O	HOH W 338	38.003	70.941	79.707	1.00	47.97
ATOM	108	O	HOH W 339	42.635	39.826	86.317	1.00	39.90
ATOM	109	O	HOH W 340	28.158	51.028	97.893	1.00	35.28
ATOM	110	O	HOH W 341	34.562	57.666	98.193	1.00	56.42
ATOM	111	O	HOH W 342	23.659	34.535	79.197	1.00	84.39
ATOM	112	O	HOH W 343	10.337	58.458	76.704	1.00	45.85
ATOM	113	O	HOH W 344	32.164	75.101	85.461	1.00	54.21
ATOM	114	O	HOH W 345	32.930	38.410	86.586	1.00	43.15
ATOM	115	O	HOH W 346	32.310	36.987	102.558	1.00	47.71
ATOM	116	O	HOH W 347	11.163	49.101	82.634	1.00	84.37
ATOM	117	O	HOH W 348	34.268	69.634	83.019	1.00	47.39
ATOM	118	O	HOH W 349	31.352	37.085	89.579	1.00	74.88
ATOM	119	O	HOH W 350	29.118	56.986	95.860	1.00	34.59
ATOM	120	O	HOH W 351	1.634	70.786	81.659	1.00	41.89
ATOM	121	O	HOH W 352	2.044	71.714	85.736	1.00	37.84
ATOM	122	O	HOH W 353	16.219	75.511	74.471	1.00	44.53
ATOM	123	O	HOH W 354	24.035	45.705	97.204	1.00	48.11
ATOM	124	O	HOH W 355	17.939	77.382	82.853	1.00	65.65
ATOM	125	O	HOH W 356	12.504	76.991	70.634	1.00	50.43
ATOM	126	O	HOH W 357	16.951	78.295	74.889	1.00	47.02
ATOM	127	O	HOH W 358	15.777	75.404	81.566	1.00	33.68
ATOM	128	O	HOH W 359	37.401	72.376	82.831	1.00	50.52
ATOM	129	O	HOH W 360	14.060	44.359	88.918	1.00	80.84
ATOM	130	O	HOH W 361	32.619	76.123	75.757	1.00	42.84
ATOM	131	O	HOH W 362	21.836	66.226	94.339	1.00	63.40
ATOM	132	O	HOH W 363	16.011	46.526	82.837	1.00	38.42
ATOM	133	O	HOH W 364	7.716	57.886	82.470	1.00	50.22

[Drawing 44]

ATOM	134	O	HOH W 365	41.813	72.155	81.960	1.00	76.60
ATOM	135	O	HOH W 366	5.810	63.614	94.440	1.00	41.72
ATOM	136	O	HOH W 367	22.833	66.006	98.308	1.00	65.79
ATOM	137	O	HOH W 368	21.384	36.791	76.692	1.00	59.29
ATOM	138	O	HOH W 369	38.765	52.950	92.219	1.00	27.87
ATOM	139	O	HOH W 370	46.430	68.991	81.609	1.00	70.52
ATOM	140	O	HOH W 371	36.973	69.709	83.153	1.00	33.81
ATOM	141	O	HOH W 372	22.238	43.716	92.825	1.00	44.49
ATOM	142	O	HOH W 373	23.096	80.189	77.308	1.00	50.73
ATOM	143	O	HOH W 374	2.790	53.932	81.478	1.00	50.22
ATOM	144	O	HOH W 375	3.292	64.768	94.055	1.00	46.64
ATOM	145	O	HOH W 376	26.937	79.257	75.755	1.00	47.21
ATOM	146	O	HOH W 377	45.046	50.594	85.873	1.00	46.10
ATOM	147	O	HOH W 378	24.988	68.312	90.158	1.00	39.03
ATOM	148	O	HOH W 379	2.045	61.203	93.643	1.00	49.73
ATOM	149	O	HOH W 380	44.273	56.110	87.700	1.00	46.74
ATOM	150	O	HOH W 381	26.747	76.462	73.043	1.00	50.91
ATOM	151	O	HOH W 382	40.545	70.889	76.918	1.00	68.80
ATOM	152	O	HOH W 383	25.523	80.486	83.807	1.00	67.90
ATOM	153	O	HOH W 384	40.972	36.296	87.372	1.00	66.49
ATOM	154	O	HOH W 385	12.617	56.710	77.567	1.00	44.81
ATOM	155	O	HOH W 386	44.460	48.054	74.082	1.00	41.02
ATOM	156	O	HOH W 387	35.781	73.896	86.117	1.00	38.14
ATOM	157	O	HOH W 388	21.625	80.398	81.815	1.00	47.96
ATOM	158	O	HOH W 389	46.628	56.635	82.977	1.00	50.89
ATOM	159	O	HOH W 390	12.308	51.573	78.083	1.00	64.92
ATOM	160	O	HOH W 391	30.773	39.420	87.798	1.00	55.92
ATOM	161	O	HOH W 392	26.088	65.110	89.923	1.00	44.80
ATOM	162	O	HOH W 393	10.719	70.886	96.928	1.00	48.46
ATOM	163	O	HOH W 394	12.474	47.243	84.457	1.00	53.08
ATOM	164	O	HOH W 395	24.296	71.312	91.828	1.00	48.39
ATOM	165	O	HOH W 396	6.459	50.108	83.133	1.00	57.82
ATOM	166	O	HOH W 397	42.423	66.213	75.196	1.00	34.97
ATOM	167	O	HOH W 398	29.045	53.518	101.769	1.00	46.59
ATOM	168	O	HOH W 399	27.195	39.655	105.406	1.00	41.59
ATOM	169	O	HOH W 400	6.834	56.385	96.211	1.00	45.81
ATOM	170	O	HOH W 401	47.957	50.138	78.280	1.00	43.60
ATOM	171	O	HOH W 402	23.330	36.461	72.787	1.00	54.41
ATOM	172	O	HOH W 403	29.051	79.533	81.900	1.00	78.87
ATOM	173	O	HOH W 404	46.670	55.026	74.340	1.00	68.61
ATOM	174	O	HOH W 405	28.985	78.746	85.840	1.00	75.16
ATOM	175	O	HOH W 406	32.117	68.589	73.365	1.00	42.10
ATOM	176	O	HOH W 407	48.677	52.842	75.727	1.00	66.77
ATOM	177	O	HOH W 408	29.185	36.245	72.017	1.00	75.24
ATOM	178	O	HOH W 409	37.168	67.596	97.670	1.00	38.24
ATOM	179	O	HOH W 410	11.986	77.352	92.370	1.00	35.94
ATOM	180	O	HOH W 411	39.548	63.174	98.280	1.00	39.58
ATOM	181	O	HOH W 412	30.500	79.967	79.292	1.00	62.87
ATOM	182	O	HOH W 413	18.003	41.205	83.764	1.00	64.48
ATOM	183	O	HOH W 414	34.455	37.242	89.080	1.00	52.58
ATOM	184	O	HOH W 415	47.074	60.938	83.746	1.00	66.98
ATOM	185	O	HOH W 416	10.880	54.535	78.559	1.00	45.29
ATOM	186	O	HOH W 417	30.230	76.830	74.341	1.00	71.09
ATOM	187	O	HOH W 418	12.118	81.147	79.341	1.00	49.66

[Drawing 45]

ATOM	188	O	HOH W 419	32.095	76.945	80.548	1.00	63.23
ATOM	189	O	HOH W 420	-0.301	68.264	84.539	1.00	48.83
ATOM	190	O	HOH W 421	10.822	64.227	102.313	1.00	81.32
ATOM	191	O	HOH W 422	23.374	42.555	101.170	1.00	42.91
ATOM	192	O	HOH W 423	20.016	59.713	74.793	1.00	38.45
ATOM	193	O	HOH W 424	15.833	78.412	79.495	1.00	56.01
ATOM	194	O	HOH W 425	43.534	35.850	84.957	1.00	63.16
ATOM	195	O	HOH W 426	11.933	68.018	98.874	1.00	52.15
ATOM	196	O	HOH W 427	20.777	37.368	85.962	1.00	57.71
ATOM	197	O	HOH W 428	22.392	36.632	89.560	1.00	68.43
ATOM	198	O	HOH W 429	29.340	37.487	101.980	1.00	74.20
ATOM	199	O	HOH W 430	23.237	39.294	91.878	1.00	74.07
ATOM	200	O	HOH W 431	13.654	75.325	94.697	1.00	73.83
ATOM	201	O	HOH W 432	27.904	38.307	96.631	1.00	57.14
ATOM	202	O	HOH W 433	44.213	59.909	79.188	1.00	37.71
ATOM	203	O	HOH W 434	2.129	75.408	79.755	1.00	64.17
ATOM	204	O	HOH W 435	13.993	43.469	84.483	1.00	59.78
ATOM	205	O	HOH W 436	31.644	55.529	99.951	1.00	58.81
ATOM	206	O	HOH W 437	9.462	82.415	76.470	1.00	48.44
ATOM	207	O	HOH W 438	21.813	58.761	98.061	1.00	60.37
ATOM	208	O	HOH W 439	22.202	59.533	93.382	1.00	43.39
ATOM	209	O	HOH W 440	18.118	43.497	86.455	1.00	46.86
ATOM	210	O	HOH W 441	13.762	54.340	105.466	1.00	57.78
ATOM	211	O	HOH W 442	33.277	73.931	83.853	1.00	56.73
ATOM	212	O	HOH W 443	34.442	68.648	90.744	1.00	27.90
ATOM	213	O	HOH W 444	30.640	67.899	91.831	1.00	53.48
ATOM	214	O	HOH W 445	40.813	44.217	74.058	1.00	53.35
ATOM	215	O	HOH W 446	33.012	71.334	90.213	1.00	53.98
ATOM	216	O	HOH W 447	25.130	57.928	101.293	1.00	38.97
ATOM	217	O	HOH W 448	7.584	82.067	74.163	1.00	26.55
ATOM	218	O	HOH W 449	42.214	40.521	78.980	1.00	37.75
ATOM	219	O	HOH W 450	8.915	57.776	101.115	1.00	50.37
ATOM	220	O	HOH W 451	15.963	42.582	79.699	1.00	71.24
ATOM	221	O	HOH W 452	23.011	77.967	75.363	1.00	64.04
ATOM	222	O	HOH W 453	36.910	35.452	88.469	1.00	70.47
ATOM	223	O	HOH W 454	37.814	55.271	99.966	1.00	54.36
ATOM	224	O	HOH W 455	26.721	58.439	99.230	1.00	86.46
ATOM	225	O	HOH W 456	16.108	40.093	81.126	1.00	98.28
ATOM	226	O	HOH W 457	27.800	35.543	96.536	1.00	63.56
ATOM	227	O	HOH W 458	5.859	51.318	95.801	1.00	68.96
ATOM	228	O	HOH W 459	7.841	51.875	96.622	1.00	64.76
ATOM	229	O	HOH W 460	28.280	66.535	89.122	1.00	73.27
ATOM	230	O	HOH W 461	13.943	46.268	81.680	1.00	56.20
ATOM	231	O	HOH W 462	14.681	69.220	73.344	1.00	83.46
ATOM	232	O	HOH W 463	30.388	71.379	89.815	1.00	60.45
ATOM	233	O	HOH W 464	8.062	56.915	75.809	1.00	59.76
ATOM	234	O	HOH W 465	30.104	41.907	101.688	1.00	61.89
ATOM	235	O	HOH W 466	4.988	49.407	95.471	1.00	61.48
ATOM	236	O	HOH W 467	8.747	53.997	77.187	1.00	79.74
END								

[Drawing 46]

A72F(s) 5'-CA-GAC-CTG-GCC-TTT-GGC-GAT-GTG-GC-3'

A72F(as) 3'-GT-CTG-GAC-CGG-AAA-CCG-CTA-CAC-CG-5'

D L A F72 G D V

A72E(s) 5'-CA-GAC-CTG-GCC-GAA-GGC-GAT-GTG-GC-3'

A72E(as) 3'-GT-CTG-GAC-CGG-CTT-CCG-CTA-CAC-CG-5'

D L A E72 G D V

[Drawing 47]

I103D(s) 5'-TG-ACC-AAT-ATG-GAC-GAG-GAC-GCC-GG-3'  
I103D(as) 3'-AC-TGG-TTA-TAC-CTG-CTC-CTG-CGG-CC-5'  
T N M D103 E D A  
T153N(s) 5'-GG-CAT-ACC-TCT-AAC-GGC-TGG-GCT-AC-3'  
T153N(as) 3'-CC-GTA-TGG-AGA-TTG-CCG-ACC-CGA-TG-5'  
H T S N153 G W A

[Drawing 48]

L140F(s) 5'-AC-CAG-GAC-AAA-TTC-TCC-AAA-AAT-GG-3'  
L140F(as) 3'-TG-GTC-CTG-TTT-AAG-AGG-TTT-TTA-CC-5'  
Q D K F140 S K N  
L140K(s) 5'-AC-CAG-GAC-AAA-AAA-TCC-AAA-AAT-GG-3'  
L140K(as) 3'-TG-GTC-CTG-TTT-TTT-AGG-TTT-TTA-CC-5'  
Q D K K140 S K N  
L140E(s) 5'-AC-CAG-GAC-AAA-GAA-TCC-AAA-AAT-GG-3'  
L140E(as) 3'-TG-GTC-CTG-TTT-CTT-AGG-TTT-TTA-CC-5'  
Q D K E140 S K N

[Translation done.]

## \* NOTICES \*

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- 1.This document has been translated by computer. So the translation may not reflect the original precisely.
- 2.\*\*\*\* shows the word which can not be translated.
- 3.In the drawings, any words are not translated.

## WRITTEN AMENDMENT

----- [Written amendment]

[Filing date]September 14, Heisei 12 (2000.9.14)

[Amendment 1]

[Document to be Amended]Specification

[Item(s) to be Amended]0050

[Method of Amendment]Change

[Proposed Amendment]

[0050]Example 20 Enterobacter aerogenes IFO 12010 Refining of origin wild type acid phosphatase and determination of N-terminal-amino-acid arrangement

Refine acid phosphatase of the Enterobacter aerogenes IFO12010 origin from the culture object of Escherichia coli JM109/pENP110 of example 24 statement of JP,10-201481,A, and N-terminal-amino-acid arrangement is determined, The amino acid sequence of maturation protein was determined. Escherichia coli JM109/pENP110 are the bacillus which introduced the acid phosphatase gene of the Enterobacter aerogenes IFO12010 origin into 109 shares of Escherichia coli JM, and produce this acid phosphatase. The amino acid sequence of the precursor protein expected from the base sequence of this acid phosphatase gene is equivalent to the arrangement shown in the array number 10 of an array table. The amino acid sequence shown in the array number 10 is an amino acid sequence of L61 Q/A63 Q/E64 A/N67 D/S69 A/G72 D/T133 K/E134 D/I151T variant EA-AP. 50 ml of nutrient media (pH 7.0) containing 1 g/dl of peptone, 0.5 g/dl of yeast extracts, and 1 g/dl of salt were put into a 500-ml Sakaguchi flask, and it heat-sterilized for 20 minutes at 120 \*\*. One platinum loop of Escherichia coli JM109/pENP110 was inoculated into this, and shaking culture was carried out at 30 \*\* for 16 hours. The biomass which collected biomasses from culture medium by centrifugal separation was suspended to the 100mM potassium phosphate buffer (pH 7.0) of 100 ml, ultrasonication was performed for 20 minutes at 4 \*\*, and the biomass was crushed. The treating solution was centrifuged and the cell-free extract was prepared except for the insoluble fraction. Ammonium sulfate was added so that it might become this cell-free extract with saturation 30%. After removing the precipitate generated by centrifugal separation, additional addition of the ammonium sulfate was carried out so that it might become digestive liquor with saturation 60%. Centrifugal separation recovered the generated precipitate and it dissolved in the 100mM potassium phosphate buffer. After dialyzing this crude enzyme liquid 3 times to 500 ml of 100mM potassium phosphate buffers (pH 7.0), It charged in DEAE-TOYOPARU 650M column (phi3.0x10.0cm) equilibrated with 20mM potassium phosphate buffer (pH 7.0), and 20mM potassium phosphate buffer (pH 7.0) washed. Since phosphate transfer activity suited the bypassing fraction, the fractions concerned were collected. Ammonium sulfate was added so that it might become this activity fraction with saturation 35%, and this was made to stick to the butyl-Toyopearl column (phi3.0x7.0cm) equilibrated with 20mM potassium phosphate buffer (pH 7.0) which contains saturated ammonium sulfate 35%. This was eluted by the linear concentration gradient of the saturated potassium phosphate buffer (pH 7.0) 20% from saturation 35%. CM-TOYOPARU equilibrated with 10mM potassium phosphate buffer (pH 6.0) after collecting activity fractions and dialyzing to 10mM potassium phosphate buffer (pH 6.0) 1L It was made to stick to a column (phi3.0x7.0cm). This was eluted by the linear concentration gradient of the

potassium phosphate buffer (pH 6.0) containing 300mM potassium chloride from 0mM. These activity fractions were collected. The above operation refined the enzyme in which phosphate transfer activity is shown about 5 times with the recovery rate of about 16% more nearly eventually than a cell-free extract. This enzyme preparation was uniform in SDS-polyacrylamide electrophoresis. It is DITC about these refining enzymes. Membrane It is made to stick to [a milli gene / bio-search (Milligen/Biosearch) company make], When the amino acid sequence of the amino terminal was determined using Prosequencer 6625 (a milli gene / bio-search company make), the amino acid sequence of the amino terminal of 5 residue shown in the array number 98 of the array table was determined. Since the amino terminal of refining enzymes was started from the 21st alanine residue of the arrangement of the array number 10 of an array table, The amino acid sequence shown in the array number 10 of an array table is the arrangement of a precursor protein, and it was thought that peptide to the 20th phenylalanine residue was removed from the 1st methionine residue after translation. From this result, the amino acid sequence of mature-bodies protein is equivalent to the arrangement shown in the amino acid numbers 1-228 during the arrangement shown in the array number 10 of an array table.

[Amendment 2]

[Document to be Amended]Specification

[Item(s) to be Amended]0062

[Method of Amendment]Change

[Proposed Amendment]

[0062]Example 23 *Enterobacter aerogenes* whose compatibility over guanosine improved IFO 12010

Phosphorylation of the guanosine by an origin new variant acid phosphatase transgenics bacillus

Each variant acid phosphatase gene. The included plasmid. introduced *Escherichia coli* .

JM109/pENP180, *Escherichia coli* JM109/pENP320, *Escherichia coli* JM109/pENP340, *Escherichia coli* JM109/pENP410, *Escherichia coli* JM109/pENP510, And *Escherichia coli* JM109/pENP520 was

inoculated into 50 ml of L culture media containing ampicillin 100microg/ml and IPTG1mM, and it

cultivated at 37 \*\* for 16 hours. 10 g/dl of pyrophoric acid and 6.6 g/dl of grinding guanosine

prepared like Example 1 of the Japanese-Patent-Application-No. No. 189226 [ 12 to ] specification

are dissolved in a 100mM acetic acid buffer (pH 4.5), It was made to react at 35 \*\* for 12 hours,

maintaining [ to this, add each biomass so that it may become 100 mg/dl by dry cell weight, and ] pH to 4.5. The quantity of generated 5'-guanylic acid was shown in Table 17. *Escherichia coli* each whose

bacillus which introduced the enzyme variant as shown in Table 17 is an old stock Productivity

improved compared with JM109/pENP180, and generation accumulation of the 5'-guanylic acid was carried out with high yield.

[Translation done.]

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(54) 【発明の名称】 変異型ヌクレオシド-5'-リン酸生産酵素

(57) 【要約】 (修正有)

【課題】 ヌクレオシド-5'-リン酸生産能が向上した新規な変異型ヌクレオシド-5'-リン酸生産酵素、その取得のための新規な手段、及び該酵素の用途を提供する。

【解決手段】 ヌクレオシド-5'-リン酸生産酵素において、Lys残基 1 個、Arg残基 2 個、His残基 2 個が存在し、これらのC $\alpha$ 間距離が特定の範囲内にあり、かつその付近にヌクレオシドが結合するスペースを有する、リン酸基転移活性及び／又はホスファターゼ活性を有する酵素のヌクレオシド-5'-リン酸生産能が向上した変異型ヌクレオシド-5'-リン酸生産酵素。既知の酵素の結晶のX線構造解析に基づく変異の確定による該酵素の製造方法。

【効果】 より活性の高い酵素の取得が容易となった。



## 【特許請求の範囲】

【請求項1】 ヌクレオシド-5' -リン酸生産酵素において、Lys残基1つ、Arg残基2つ、His残基2つが存在し、これらのC $\alpha$ 間距離が図1に示す範囲内にあり、かつその付近にヌクレオシドが結合するスペースを有する、リン酸基転移活性及び／又はホスファターゼ活性を有する酵素のヌクレオシド-5' -リン酸生産能が向上した変異型ヌクレオシド-5' -リン酸生産酵素。

【請求項2】 酵素の由来がエシェリヒア属細菌、モルガネラ属細菌、プロビデンシア属細菌、エンテロバクター属細菌、クレブジエラ属細菌、又はエンテロバクター属細菌に属するものである請求項1に記載の変異型ヌクレオシド-5' -リン酸生産酵素。

【請求項3】 エシェリヒア・ブラッタエ由来酸性ホスファターゼの結晶をX線結晶構造解析して得られる原子座標データに示されている構造座標を元にして、イノシン、グアノシン等のヌクレオシド並びにそのリン酸化合物との結合様式を推定し、アミノ酸残基及び／又は補欠因子等の置換、追加、削除によりヌクレオシド-5' -リン酸生産能が向上した請求項1記載の変異型ヌクレオシド-5' -リン酸生産酵素。

【請求項4】 エシェリヒア・ブラッタエ由来酸性ホスファターゼのアミノ酸配列の以下の位置（エシェリヒア・ブラッタエ酸性ホスファターゼのSer72、又はSer72から10Å以内にある残基）：16、67-76、78-79、96、99-100、102-104、106-108、115、140、148-154、157、179、183の少なくとも一つの位置に変化が生じている変異型ヌクレオシド-5' -リン酸生産酵素。

【請求項5】 リン酸基転移活性及び／又はホスファターゼ活性を有する酵素で、エシェリヒア・ブラッタエ由来酸性ホスファターゼとのアミノ酸配列アラインメントをしたときに、エシェリヒア・ブラッタエ由来酸性ホスファターゼのアミノ酸配列の以下の位置（エシェリヒア・ブラッタエ酸性ホスファターゼのSer72、又はSer72から10Å以内にある残基）：16、67-76、78-79、96、99-100、102-104、106-108、115、140、148-154、157、179、183に対応する少なくとも一つの位置に変化が生じている変異型ヌクレオシド-5' -リン酸生産酵素。

【請求項6】 リン酸基転移活性及び／又はホスファターゼ活性を有する酵素で、エシェリヒア・ブラッタエ由来酸性ホスファターゼの3次元構造とのアラインメントをトレッキング法により行ったときに、エシェリヒア・ブラッタエ由来酸性ホスファターゼのアミノ酸配列の以下の位置（エシェリヒア・ブラッタエ酸性ホスファターゼのSer72、又はSer72から10Å以内にある残基）：16、67-76、78-79、96、99-100、102-104、106-108、115、14

0、148-154、157、179、183に対応する少なくとも一つの位置に変化が生じている変異型ヌクレオシド-5' -リン酸生産酵素。

【請求項7】 酵素の由来がエンテロバクター・アエロゲネス由来であり、そのアミノ酸配列において14番目のロイシン残基、61番目のロイシン残基、63番目のアラニン残基、64番目のグルタミン酸残基、67番目のアスパラギン残基、69番目のセリン残基、70番目のアラニン残基、71番目のグリシン残基、72番目のグリシン残基、101番目のイソロイシン残基、102番目のグルタミン酸残基、133番目のスレオニン残基、134番目のグルタミン酸残基、138番目のロイシン残基、149番目のスレオニン残基、151番目のイソロイシン残基のうち少なくとも一つのアミノ酸残基が他のアミノ酸残基に置換されたものである変異型ヌクレオシド-5' -リン酸生産酵素。

【請求項8】 リン酸基転移活性及び／又はホスファターゼ活性を有する酵素、あるいはそれとモリブデン酸との複合体の結晶をX線結晶構造解析して得られる立体構造から確定された、該酵素の活性部位、及び／又はそれから10Å以内にあるアミノ酸残基を、置換、追加、削除をすることにより、ヌクレオシド-5' -リン酸生産能が向上した変異型酵素を製造することを特徴とする変異型ヌクレオシド-5' -リン酸生産酵素の製造方法。

【請求項9】 エシェリヒア・ブラッタエ由来酸性ホスファターゼの構造座標を使用して、ホスファターゼ又はリン酸基転移酵素の阻害剤を製造する方法。

【請求項10】 リン酸基転移活性及び／又はホスファターゼ活性を有する酵素、あるいはそれとモリブデン酸との複合体のいずれかの結晶。

【請求項11】 六方晶系の空間群P6<sub>3</sub>22を有する、エシェリヒア・ブラッタエ由来酸性ホスファターゼの結晶。

【請求項12】 斜方晶系の空間群P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>を有する、エシェリヒア・ブラッタエ由来酸性ホスファターゼG74D／I153T変異型酵素の結晶。

【請求項13】 三方晶系の空間群P3<sub>1</sub>21を有する、エシェリヒア・ブラッタエ由来酸性ホスファターゼとモリブデン酸との複合体（反応中間体アナログ）の結晶。

【請求項14】 請求項1～7のいずれか1項に記載の酵素をコードする遺伝子。

【請求項15】 請求項14に記載の遺伝子を含む組換えDNA。

【請求項16】 請求項15に記載の組換えDNAを保有する微生物。

【請求項17】 請求項1～7のいずれか1項に記載の酵素、又はそれを含有する微生物、あるいは請求項16に記載の微生物を、ヌクレオシド並びにリン酸供与体に作用させてヌクレオシド-5' -リン酸を生成させ、こ

れを採取することを特徴とするヌクレオシド-5'-リン酸の製造方法。

#### 【発明の詳細な説明】

##### 【0001】

【発明の属する技術分野】本発明は、ヌクレオシド-5'-リン酸生産能が向上した変異型ヌクレオシド-5'-リン酸生産酵素、及びその製造方法に関する。また、本発明は、上記した酵素の製造に有用な酵素類に関する。更に本発明は、ヌクレオシド-5'-リン酸の製造方法に関し、またその製造方法に有用な、前記の変異型酵素をコードする遺伝子、該遺伝子を含む組換えDNA、該組換えDNAを保有する微生物に関する。ヌクレオシド-5'-リン酸は、調味料、医薬並びにそれらの原料として有用である。なお、本発明は、X線結晶構造解析技術により蛋白質の新規立体構造の解明に成功したことに基づくと共に、該立体構造は微生物に限らない発展性を有する。

##### 【0002】

【従来の技術】ヌクレオシドを生化学的にリン酸化してヌクレオシド-5'-リン酸を安価かつ効率的に製造する方法として、特定の微生物菌体を、酸性条件下でヌクレオシド並びにポリリン酸（塩）、フェニルリン酸（塩）及びカルバミルリン酸から成る群より選択されるリン酸供与体に作用させることにより、ヌクレオシド-2'-リン酸、ヌクレオシド-3'-リン酸異性体の副生を伴うことなくヌクレオシド-5'-リン酸を効率よく生成する方法が開発されている（特開平7-231793号）。その後、エシェリヒア・ブラッタエ（*Escherichia blattae*）及びモルガネラ・モルガニ（*Morganella morganii*）より酸性ホスファターゼをコードする遺伝子を取得し、遺伝子工学的に該遺伝子をエシェリヒア・コリで大量発現することによりヌクレオシド-5'-リン酸の生産性が更に向上することが確認された。該酸性ホスファターゼの構造を図2に示す。すなわち、図2は、エシェリヒア・ブラッタエ由来酸性ホスファターゼ（以下、EB-APと略記する）のアミノ酸配列を、モルガネラ・モルガニ、サルモネラ・チフィウム（*Salmonella typhimurium*）、ザイモナス・モビリス（*Zymomonas mobilis*）由来酸性ホスファターゼのアミノ酸配列とアラインメントした図である。それぞれの酸性ホスファターゼの遺伝子の塩基配列と、コードされる酵素のアミノ酸配列を、配列表の配列番号1～8に示す。図2で星印は保存された残基を示す。2次構造の領域をアラインメントの上に棒で示した。四角の線で囲んだ部分は、酸性ホスファターゼファミリーの間で共通しているモチーフを示す。モチーフは、1) KXXXXXXRP配列番号121、2) PSQH配列番号122、3) SRXXXXHXXD配列番号123、の3つのドメインから成り立っている。ここで、Xは任意のアミノ酸である。該酸性ホスファターゼ（図2）は、リン酸基転移活性を有するものの、野

生型においては、ヌクレオシド-5'-リン酸をヌクレオシドに分解するホスファターゼ活性が優勢であり、蓄積されたヌクレオシド-5'-リン酸が分解されてしまう欠点があった。そこで、ランダムに多数の変異型酵素を発生させ、その中からホスファターゼ活性に比してリン酸基転移活性が相対的に向上した変異型酸性ホスファターゼが見出され、該変異型酸性ホスファターゼ遺伝子を大量発現させることによりヌクレオシド-5'-リン酸の生産性が飛躍的に向上することが示された（特開平9-37785号）。該変異型ホスファターゼは、ヌクレオシドに対する親和性が向上しており、それによりリン酸基転移活性が改善されたと考えられる。上記のエシェリヒア・ブラッタエ由来変異型酸性ホスファターゼ（＝G74D/I153T変異型酵素）は、モルガネラ・モルガニ由来酸性ホスファターゼ（MM-AP）の対応するG72D/I151T変異型酵素よりリン酸基転移活性が弱い、8つのアミノ酸残基を一次構造上対応するMM-APのアミノ酸に置換した10残基置換L63Q/A65Q/E66A/N69D/S71A/S72A/G74D/T135K/E136D/I153T変異型酵素（以降、単に10残基置換変異型EB-APと記述）は、G72D/I151T変異型MM-APとほぼ同等のリン酸基転移活性を得ることが示された（特開平10-201481号）。

##### 【0003】

【発明が解決しようとする課題】上述の生産性が向上したエシェリヒア・ブラッタエ由来酸性ホスファターゼ（EB-AP）のG74D/I153T変異型酵素遺伝子、更には10残基置換変異型酵素遺伝子をエシェリヒア・コリで大量発現することによりヌクレオシド-5'-リン酸を生産する方法が確立された（特開平9-37785号、特開平10-201481号）が、更に生産性の向上した変異型EB-APが望まれる。本発明は、EB-APの3次元構造に基づいて、変異型EB-APを設計することにより、ヌクレオシド-5'-リン酸生産性の更なる向上を図ることを課題とする。

##### 【0004】

【課題を解決するための手段】本発明を概説すれば、下記に列挙するとおりである。

(1) ヌクレオシド-5'-リン酸生産酵素において、Lys残基1つ、Arg残基2つ、His残基2つが存在し、これらのC $\alpha$ 間距離が図1に示す範囲内にあり、かつその付近にヌクレオシドが結合するスペースを有する、リン酸基転移活性及び/又はホスファターゼ活性を有する酵素のヌクレオシド-5'-リン酸生産能が向上した変異型ヌクレオシド-5'-リン酸生産酵素。

(2) 酵素の由来がエシェリヒア属細菌、モルガネラ属細菌、プロビデンシア属細菌、エンテロバクター属細菌、クレブジエラ属細菌、又はエンテロバクター属細菌に属するものである(1)項記載の変異型ヌクレオシド

ー 5' - リン酸生産酵素。

(3) E B - A P の結晶を X 線結晶構造解析して得られる原子座標データに示されている構造座標を元にして、イノシン、グアノシン等のヌクレオシドとの結合様式を推定し、アミノ酸残基及び／又は補欠因子等の置換、追加、削除をすることによりヌクレオシドー 5' - リン酸生産能が向上した (1) 項記載の変異型ヌクレオシドー 5' - リン酸生産酵素。

(4) E B - A P のアミノ酸配列の以下の位置 (E B - A P のアミノ酸 Ser 72、又は Ser 72 から 10 Å 以内にある残基) : 16、67-76、78-79、96、99-100、102-104、106-108、115、140、148-154、157、179、183 の少なくとも一つの位置に変化が生じている変異型ヌクレオシドー 5' - リン酸生産酵素。

(5) リン酸基転移活性及び／又はホスファターゼ活性を有する酵素で、E B - A P とのアミノ酸配列アラインメントをしたときに、E B - A P のアミノ酸配列の以下の位置 (E B - A P のアミノ酸 Ser 72、又は Ser 72 から 10 Å 以内にある残基) : 16、67-76、78-79、96、99-100、102-104、106-108、115、140、148-154、157、179、183 の少なくとも一つの位置に変化が生じている変異型ヌクレオシドー 5' - リン酸生産酵素。

(6) リン酸基転移活性及び／又はホスファターゼ活性を有する酵素で、E B - A P の 3 次元構造とのアラインメントをトレディング法により行ったときに、E B - A P のアミノ酸配列の以下の位置 (E B - A P のアミノ酸 Ser 72、又は Ser 72 から 10 Å 以内にある残基) : 16、67-76、78-79、96、99-100、102-104、106-108、115、140、148-154、157、179、183 の少なくとも一つの位置に変化が生じている変異型ヌクレオシドー 5' - リン酸生産酵素。

【0005】(7) 酵素の由来がエンテロバクター・アエロゲネス由来であり、そのアミノ酸配列において 14 番目のロイシン残基、61 番目のロイシン残基、63 番目のアラニン残基、64 番目のグルタミン酸残基、67 番目のアスパラギン残基、69 番目のセリン残基、70 番目のアラニン残基、71 番目のグリシン残基、72 番目のグリシン残基、101 番目のイソロイシン残基、102 番目のグルタミン酸残基、133 番目のスレオニン残基、134 番目のグルタミン酸残基、138 番目のロイシン残基、149 番目のスレオニン残基、151 番目のイソロイシン残基のうち少なくとも一つのアミノ酸残基が他のアミノ酸残基に置換されたものである変異型ヌクレオシドー 5' - リン酸生産酵素。

(8) リン酸基転移活性及び／又はホスファターゼ活性を有する酵素、あるいはそれとモリブデン酸との複合体の結晶を X 線結晶構造解析して得られる立体構造から

確定された、該酵素の活性部位に位置するアミノ酸残基 (Lys 1 つ、Arg 2 つ、His 2 つにより構成される)、及び／又はそれから 10 Å 以内にあるアミノ酸残基を、置換、追加、削除をすることにより、ヌクレオシドー 5' - リン酸生産能が向上した変異型酵素を製造することを特徴とする変異型ヌクレオシドー 5' - リン酸生産酵素の製造方法。

(9) エシェリヒア・ブラッタエ由来酸性ホスファターゼの構造座標を使用して、ホスファターゼ又はリン酸基転移酵素の阻害剤を製造する方法。

【0006】(10) リン酸基転移活性及び／又はホスファターゼ活性を有する酵素、あるいはそれとモリブデン酸との複合体のいずれかの結晶。

(11) 六方晶系の空間群  $P6_322$  を有する、E B - A P の結晶。

(12) 斜方晶系の空間群  $P2_12_12_1$  を有する、E B - A P G74D / I153T 変異型酵素の結晶。

(13) 三方晶系の空間群  $P3_121$  を有する、E B - A P とモリブデン酸との複合体 (反応中間体アナログ) の結晶。

【0007】(14) (1) ~ (7) 項のいずれか 1 項に記載の酵素をコードする遺伝子。

(15) (14) 項に記載の遺伝子を含む組換え DNA。

(16) (15) 項に記載の組換え DNA を保有する微生物。

【0008】(17) (1) ~ (7) 項のいずれか 1 項に記載の酵素、又はそれを含有する微生物、あるいは (16) 項に記載の微生物を、ヌクレオシド並びにリン酸供与体に作用させてヌクレオシドー 5' - リン酸を生成させ、これを採取することを特徴とするヌクレオシドー 5' - リン酸の製造方法。

【0009】本発明は、E B - A P の 3 次元構造を基に、ヌクレオシドとの結合様式モデルを構築し、それに基づき設計した変異型 E B - A P を利用したヌクレオシドー 5' - リン酸の生産方法を提供する。

【0010】

【発明の実施の形態】以下、本発明を具体的に説明する。

(1) X 線結晶構造解析により蛋白質の 3 次元構造を決定するには、蛋白質を結晶化する必要がある (実施例 1-3 に詳細を示した)。蛋白質を結晶化するためには、pH、バッファの種類、バッファの濃度、沈殿剤の種類、沈殿剤の濃度、金属等の添加剤の濃度、蛋白質の濃度、蛋白質の純度、等、数多くのパラメーターを試行錯誤により決定しなくてはならない。したがって、結晶を得るまでに数ヶ月~数年の時間がかかるのが通常であり、多大な労力に反して結晶が得られないケースも多々ある。結晶化は、3 次元構造決定のためには欠かせないが、それ以外にも、蛋白質の高純度の精製法、高密

度でプロテアーゼ抵抗性の強い安定な保存法、更には酵素の固定化利用に先立つプロセスとして産業上の有用性もある。

(2) 作製した結晶にX線を照射して回折データを収集する。蛋白質結晶はX線照射によりダメージを受け回折能が劣化するケースが多々ある。その場合、結晶を急激に $-173^{\circ}\text{C}$ 程度に冷却し、その状態で回折データを収集する低温測定が最近普及しつつある。なお、冷却に際しては、結晶が崩壊せず系全体がガラス状になるよう溶媒組成を工夫する必要がある。

(3) 結晶構造解析を行うには、回折データに加えて、位相情報が必要になる。EBAPは、類縁の蛋白質の立体構造が未知であるため、重原子同型置換法により位相問題が解決されなくてはならない。重原子同型置換法は、水銀や白金等原子番号が大きな金属原子を結晶に導入し、金属原子の大きなX線散乱能のX線回折データへの寄与を利用して位相情報を得る方法である。野生型EBAPの立体構造が決定されれば、変異型酵素及び反応中間体アナログ等類縁体の結晶構造は、それを用いた分子置換法により決定できる。分子置換法は、結晶構造を決定したい蛋白質に類縁の蛋白質の立体構造が既知の場合、その立体構造を利用して構造決定を行う手法である。例えば、ある蛋白質の野生型の立体構造が分かっているならば、その変異型蛋白質や化学修飾された蛋白質の結晶構造決定には、分子置換法が適用できる。G74D/I153T変異型EBAPについては、2ヶ所のアミノ酸置換によるヌクレオシド親和性向上の分子機構解明のために結晶構造を決定する。反応中間体アナログについては、ヌクレオシドとの結合様式モデルを構築するために結晶構造を決定する。ヌクレオシドは、供与されるリン酸基が共有結合した状態のEBAP、すなわち反応中間体に結合した後、ヌクレオシド $5'$ -リン酸に変換される。EBAPの反応中間体は不安定なので、その構造を捉えることができないが、リン酸の代りにモリブデン酸が共有結合した反応中間体アナログであれば加水分解されることがないので構造決定可能と考えた。実施例4、6、7に詳細を示した。

【0011】(4) コンピューターグラフィックス(CG)上で、反応中間体アナログの3次元構造におけるモリブデン酸結合位置を基に、その付近の窪みにヌクレオシドをフィットさせ、結合様式モデルを構築する(図3)。モデルの構築には、例えばMSI社(アメリカ)のQUANTA, INSIGHT IIの様なプログラムを利用する。なお、図3は、上記の結合様式モデルの結晶構造を示す写真である。実施例5、8に詳細を示した。

(5) 結合モデルを良く観察し、ヌクレオシドとの親和性を増大させる変異を設計する。親和性を向上させるには、疎水相互作用・静電相互作用・水素結合・ $\pi$ - $\pi$ 相互作用(芳香環の環電流が発生する磁場同士の相互作用)・CH/ $\pi$ 相互作用(芳香環の環電流とメチル基の

電子が発生する磁場の相互作用)を増強する手段が考えられる。Ser72はヌクレオシドの塩基と最も強く相互作用すると予測されるため、Phe、Tyr、Trpへの置換は疎水性相互作用及び $\pi$ - $\pi$ 相互作用を、Val、Ile、Leuへの置換は疎水性相互作用及びCH/ $\pi$ 相互作用をGlu、Aspへの置換は静電相互作用及び水素結合を増強するものと思われる。また、他のアミノ酸への置換、特により長鎖の側鎖を有するアミノ酸への置換によっても疎水性相互作用等が増強される可能性がある。Leu16、Ser71、Ser73、Glu104をPhe、Tyr、Trpに置換することによっても置換されたアミノ酸残基の芳香環とヌクレオシドの塩基との間に $\pi$ - $\pi$ 相互作用が形成されることが期待される。またIle103やThr153をより長鎖の親水性残基に置換することによりヌクレオシドのリボースとの水素結合の形成が期待される。更に、ヌクレオシド結合部位の近くに位置し、蛋白質内部に埋もれているThr151をSer、Ala、Glyといった小さな側鎖を持ったアミノ酸残基に置換すれば、蛋白質内部に空隙が生じるために、ヌクレオシド結合部位の柔軟性が増し、ヌクレオシドとの結合により適したコンフォメーションを取れるのではないかと期待される。なお、Leu140は、Ser72から $10\text{\AA}$ 以上離れているが、反応中間体アナログの立体構造において、リン酸結合部位の直近に位置する。したがって、この残基を置換すれば、反応中間体におけるリン酸結合部位周辺の構造が変化し、ひいては、ヌクレオシド結合部位の構造と揺らぎにも影響が及ぶものと考えられた。この残基を、よりかさ高いPhe、正電荷を有するLys、負電荷を有するGlu、に置換すれば、ヌクレオシドとの親和性が変化するのではないかと期待される。上記の変異は、当初はG74D/I153T変異型EBAPに対して導入する。しかし、導入の対象とする変異型酵素は、G74D/I153T変異型EBAPに限られるものではない。例えば、10残基置換変異型EBAPに変異を導入することも可能である。変異は、G74D/I153T変異型EBAPに対して導入することにする。この場合、作製される変異型酵素は、3残基置換変異型酵素となる。実施例9に詳細を示した。

(6) PCR法により、変異型EBAPをコードする遺伝子を含むプラスミドを作製する。プラスミドをエシェリヒア・コリ(Escherichia coli) JM109に導入し、変異型EBAPを生産させる。変異型EBAPのイノシンに対する親和性の指標になるKm値、及びイノシンを $5'$ -イノシン酸に変換するリン酸基転移活性を測定し、変異型EBAPの性能を評価する。ヌクレオシド $5'$ -リン酸の生産量は、多分にKm値に依存すると考えられる。ピロリン酸がEBAPと反応し、リン酸イオンが離脱し、リン酸基がEBAPと共有結合した形の反応中間体が形成された後、水分子がこれを攻撃すれば、リン酸基が外れてしまう(ホスファタ

一ゼ反応)。ピロリン酸は、ヌクレオシド-5'-リン酸を生成せずに無駄に消費されたことになる。一方、ヌクレオシドが反応中間体を攻撃すれば、リン酸基はヌクレオシドとホスホモノエステル結合を形成し、生成したヌクレオシド-5'-リン酸がEB-APから離脱する(リン酸基転移反応)。ピロリン酸はヌクレオシド-5'-リン酸生成に活用されたことになる。つまり、反応中間体を水とヌクレオシドが取り合い水が勝てばホスファターゼ活性が、ヌクレオシドが勝てばリン酸基転移活性が、発揮されることになる。ヌクレオシドのEB-APに対する親和性が上昇すれば、すなわち、Km値が低下すれば、リン酸基転移反応が行われる可能性が高くなる。また、リン酸結合部位付近の疎水性を高め、水が近づきにくくなれば、ホスファターゼ活性が弱まり、リン酸基転移活性が相対的に強まることになる。実施例10に詳細を示した。

(7) Km値が低下し、かつリン酸基転移活性が上昇した変異型EB-AP遺伝子を含むプラスミドを導入したエシェリヒア・コリJM109を用いて、イノシンから5'-イノシン酸を生産する実験を行う。30℃で45時間反応を行い5'-イノシン酸生産量の経時変化をモニターする。実施例12に詳細を示した。

(8) Kmを低下させる変異箇所が見出されたら、複数の残基を組合せることによって更にヌクレオシドに対する親和性が向上し、生産性の高くなった変異型酵素を作製することができる。累加的に部位特異的変異を繰り返すことで複数の変異部位を導入することができる。また部位特異的変異の導入の際に、変異を導入するアミノ酸残基をコードする塩基の部分にミックス塩基となったプライマーを用いると特定のアミノ酸残基がすべてのアミノ酸に置換された変異型遺伝子のライブラリーを作成することができる。複数の部位にミックス塩基のプライマーを用いて変異を導入すると非常に多種類の変異型酵素をコードする変異型遺伝子のライブラリーを作成することができる。このようにして構築した遺伝子のライブラリーをエシェリヒア・コリに導入し、発現させたライブラリーから高活性のアミノ酸置換が組合せられた変異体を選び出す方法も有効である。

【0012】EB-AP以外でも、EB-APと同様の活性部位及びヌクレオシドが結合しうるスペースを持つ

酵素であれば、ヌクレオシド-5'-リン酸の生産に利用できるポテンシャルがある。活性部位は、活性に必須なアミノ酸残基を有し、かつ、それらが適切な空間的位置関係で配置されていなくてはならない。EB-APにおいては、Lys115, Arg122, His150, Arg183, His189が活性に必須であり、これら5残基のC $\alpha$ 間距離によって空間的位置関係を規定することが可能である。本発明においては、野生型、G74D/I153T変異型、反応中間体アナログの3つのEB-AP結晶構造を決定したので、それぞれの構造における活性残基のC $\alpha$ 原子間距離を測り、表1を作成した。表1の各々の距離分布が約1Åの幅を持つことから、最短距離より1Å短い距離(表1、下限)以上、最長距離より1Å長い距離(表1、上限)以下であれば、求められる活性部位を形成できるものと考えた。図1に、5つの残基の位置関係を上限、下限のC $\alpha$ 間距離と共に示した。なお、EB-APの類縁酵素であるMM-APにおいて、活性残基間のすべての原子間距離が、EB-APの立体構造から規定した範囲におさまっていることが確認されたことを実施例15に示した。本実施例では、野生型ではなく、G72D/I151T変異型の例を示したが、同じ酵素の野生型と変異型で、活性部位の立体構造に大きな違いはないと考えられる。この推測は、EB-APの野生型とG74D/I153T変異型の活性部位の構造が基本的に同じであることにより支持される(表1参照)。ヌクレオシドをリン酸化して、ヌクレオシド-5'-リン酸に変換するには、上記の5残基から成る活性部位だけでは不十分で、ヌクレオシドが適切な位置に結合できなくてはならない。EB-APの場合は、リン酸基の結合部位付近に、ヌクレオシドが結合するのに適した溝状のスペースが分子表面に存在する〔(図3)：添付した原子座標を示す図10～図45を用いて、コンピュータグラフィックス(CG)上で表示できる。〕この溝は、Leu16、Ser72、Glu104、His189の4残基によって囲まれるスペースとして規定される。活性部位を有していても、ヌクレオシドが結合する適切なスペースがない酵素は、ヌクレオシド-5'-リン酸生産酵素としては不適である。

【0013】

【表1】

		野生型	G74D/I153T 変異型	反応中間体 アナログ	下限	上限
Lys115	Arg122	11.6Å	11.6Å	11.4Å	10.4Å	12.6Å
	His150	12.4Å	12.3Å	12.8Å	11.3Å	13.8Å
	Arg183	16.4Å	16.3Å	15.5Å	14.5Å	17.4Å
	His189	12.6Å	12.1Å	11.7Å	10.7Å	13.6Å
Arg122	His150	13.2Å	13.6Å	14.2Å	12.2Å	15.2Å
	Arg183	10.4Å	10.5Å	10.8Å	9.4Å	11.8Å
	His189	5.6Å	5.5Å	5.7Å	4.5Å	6.7Å
His150	Arg183	8.4Å	8.8Å	7.7Å	6.7Å	9.8Å
	His189	9.8Å	10.0Å	10.0Å	8.8Å	11.0Å
Arg183	His189	5.5Å	5.8Å	5.7Å	4.5Å	6.8Å

【0014】また、本発明は、Ser72の他のアミノ酸への置換、好ましくはPhe、Tyr、Trp、Val、Leu、Glu、Asp、Gln、Met、Thr、Arg、Lysのいずれか一つのアミノ酸への置換、を施した変異型EB-A Pを提供する。更に、Ser72から10Å以内にある残基（残基番号：16、70-71、73-76、100、102-104、106-108、115、148-154、183）はヌクレオシドと相互作用する可能性が非常に高く、これらアミノ酸残基の他のアミノ酸への置換を施した変異型EB-A Pを提供する。ここで置換とは、人為的にアミノ酸を置換した場合のみならず、自然界において置換が生じたEB-A Pと同じ酵素ファミリーに属する他の酸性ホスファターゼを選抜することも包含する。ただし、本発明は、上記のアミノ酸残基以外の変異点を含む変異型EB-A Pも提供できる。

【0015】また、EB-A Pと同じ酵素ファミリーに属する他の酸性ホスファターゼにおいても、相同のアミノ酸変異を施せば、ヌクレオシド-5' -リン酸の製造に利用することが可能である。ただし、EB-A Pのアミノ酸残基が、他の酸性ホスファターゼにおいて同じ番号のアミノ酸残基に対応するとは限らない。例えば、EB-A PのSer72は、MM-A PにおいてはAla70に対応する。2つの異なった蛋白質のアミノ酸残基の対応付けは、両者のアミノ酸配列の相同性が20%程度以上であればアミノ酸配列同士のアラインメント（Sequence Alignment）、20%程度以下であれば3次元構造とアミノ酸配列のアラインメント（Threading）により判明する。前者はBLAST等、後者はINSIGHT II等のプログラムにより実行が可能である。BLASTを用いた、EB-A Pとエンテロバクター・アエロゲネス（Enterobacter aerogenes）由来酸性ホスファターゼ（EA-A P）のアミノ酸配列アラインメントを実施例14に示した。BLASTは、FTPを使って、ncbi.nlm.nih.govよりblast/executableに存在するファイルのうち、使用するコンピューターに則したファイル入手すればよい。操作法につい

ては、<http://genome.nhgri.nih.gov/blastall/blast#install>に詳細が記述されている。

【0016】ヌクレオシド-5' -リン酸生産能向上は、ヌクレオシドとの親和性向上により達成されるケースが多いが、それ以外にも、至適pHのシフト、熱安定性の向上、等によっても達成されうる。至適pHのシフトは、活性残基のpKを変えることで達成できる〔プロテイン エンジニアリング(Protein Engng.)、第1巻、第383~388頁(1998)〕。熱安定性の向上は、プロリン残基の導入、左巻きヘリックス構造を取る残基のグリシン残基への置換〔プロテイン エンジニアリング、第6巻、第85~91頁(1993)〕、蛋白質内部の空隙を埋めること〔バイオケミストリー(Biochemistry)、第32巻、第6171~6178頁(1993)〕等により達成可能である。以上詳細に説明したように、該立体構造はヌクレオシドの親和性が向上し、ヌクレオシド-5' -リン酸生産能の向上した変異体を作製するために有効であるが、該立体構造は酵素のヌクレオシドに対する親和性のみならず、リン酸供与体との親和性を変化させるのにも有効である。特開平9-37785号公報に記載されているように該酵素はポリリン酸（塩）、フェニルリン酸（塩）、アセチルリン酸（塩）及びカルバミルリン酸（塩）等各種リン酸エステル化合物をリン酸供与体として利用することが可能であるが、ヌクレオシドとの親和性を増大させる変異を設計したのと同様の方法にて、リン酸エステル化合物との親和性を増大させる変異を設計することで、リン酸供与体の基質特異性を広げたり、リン酸の利用率を向上させることが可能である。

#### 【0017】

【実施例】以下、本発明を実施例により更に具体的に説明するが、本発明はこれらの実施例に限定されない。

【0018】実施例1 野生型EB-A Pの結晶化  
ハンギングドロップ法での蒸気拡散を利用して結晶化を行った。野生型EB-A P（濃度10mg/ml）を含むリン酸ナトリウムの20mM緩衝液（pH8.0）と、

45 (w/v%) のポリエチレングリコール400を含むトリス塩酸の100mM緩衝液を同量ずつ(各々7~10 $\mu$ l)、シリコナイゼーションしたカバーガラス上に滴下混合し、45 (w/v%) のポリエチレングリコール400を含むトリス塩酸の100mM緩衝液500 $\mu$ lを満たしたウエル(well)の上に混合液滴が釣り下がるようにかぶせ、20℃にて静置した。2、3日後に結晶が析出し、1週間から2週間後には測定可能な大きさ(0.3 $\times$ 0.3 $\times$ 1.2mm程度)の六角柱状の結晶に成長した。X線データ測定の際には、50 (w/v%) のポリエチレングリコール400を含むトリス塩酸の100mM緩衝液(pH8.0)に結晶を移した。この結晶は、取扱い上、次の点に留意する必要がある。

1) 液滴(ドロップレット)から、結晶を取り出す際に容器や用具に接触することで結晶が非常に崩れやすいため、シッティングドロップ法の結晶化形態は用いることが出来ず(結晶は成長するが)、ここで述べたハンギングドロップ法を用いた。2) 常温測定では、測定中に結晶が劣化し、徐々に分解能が下がるため、低温条件下での測定が必要であった。結晶をステージにマウントするまでの時間を極力短くし、空気にさらさないように工夫した。(株)リガクのX線回折装置R-Axis IIcを用いて、X線回折データを収集し、結晶学的パラメーターを決定した。空間群はP6<sub>3</sub>22、格子定数は、a=b=124.4Å、c=97.7Åとなった。非対称単位に分子量25000のサブユニットを一つ含むと仮定すると、結晶の水分含有率は72%となる。

【0019】実施例2 G74D/I153T変異型EB-Apの結晶化

ハンギングドロップ法での蒸気拡散を利用して結晶化を行った。G74D/I153T変異型酵素(濃度20mg/ml)を含むトリス塩酸の20mM緩衝液(pH8.0)と、38 (w/v%) のポリエチレングリコール400を含むトリス塩酸の20mM緩衝液を同量ずつ(各々5 $\mu$ l)、シリコナイゼーションしたカバーガラス上に滴下混合し、38 (w/v%) のポリエチレングリコール400を含むトリス塩酸の20mM緩衝液500 $\mu$ lを満たしたウエルの上に混合液滴が釣り下がるようにかぶせ、20℃にて静置した。2、3日後に結晶が析出し、1週間後には測定可能な大きさ(0.7 $\times$ 0.4 $\times$ 0.2mm程度)の板状結晶に成長した。X線データ測定の際には、50 (w/v%) のポリエチレングリコール400を含むトリス塩酸の100mM緩衝液(pH8.0)に結晶を移した。(株)リガクのX線回折装置R-Axis IIcを用いて、X線回折データを収集し、結晶学的パラメーターを決定した。空間群はP2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>、格子定数はa=138.0Å、b=168.3Å、c=58.2Åとなった。非対称単位に分子量150000の6量体分子を一つ含むと仮定すると、結晶の水分含有率は64%となる。

【0020】実施例3 野生型EB-Apとモリブデン酸との複合体(反応中間体アナログ)の結晶化

シッティングドロップ法での蒸気拡散を利用した共結晶化法を用いて結晶化を行った。野生型EB-Ap(濃度10mg/ml)を含むリン酸ナトリウムの20mM緩衝液(pH8.0)と、40 (w/v%) のポリエチレングリコール400、及び1mMのモリブデン酸ナトリウムを含むトリス塩酸の100mM緩衝液を同量ずつ(各々15 $\mu$ l)を、40 (w/v%) のポリエチレングリコール400を含むトリス塩酸の100mM緩衝液(pH8.0)500 $\mu$ lを満たしたウエルに設置したブリッジの窪みに滴下混合し、20℃にて静置した。2~3日後に結晶が析出し、1週間から2週間後には測定可能な大きさ(0.3 $\times$ 0.3 $\times$ 0.3mm程度)の菱餅状の結晶に成長した。X線データ測定の際には、50 (w/v%) のポリエチレングリコール400を含むトリス塩酸の100mM緩衝液(pH8.0)に結晶を移した。(株)リガクのX線回折装置R-Axis IIcを用いて、X線回折データを収集し、結晶学的パラメーターを決定した。空間群はP3<sub>1</sub>21、格子定数はa=b=86.6Å、c=205.3Åとなった。非対称単位に分子量25000のサブユニットを3つ含むと仮定すると、結晶の水分含有率は58%となる。

【0021】実施例4 野生型EB-Apの結晶構造解析

最高1.9Å分解能データまでのX線回折データを測定した。結晶は、常温においては、X線の照射によるダメージが激しかったので、-173℃に急速冷却して測定を行った。重金属塩類の溶液中に結晶を浸すことにより、重原子誘導体のスクリーニングを行った。重原子誘導体結晶の回折データはリガクR-Axis IIcを用いて得た。ネイティブデータとの差フーリエ図より、K<sub>2</sub>PtCl<sub>4</sub>が良好な重原子同型結晶を与えることを見出した。プログラムRSPSを用いることにより、K<sub>2</sub>PtCl<sub>4</sub>の唯一のプラチナ結合部位の座標を求めた。この座標をプログラムMLPHAREにより精密化し、それから計算される位相を求めた。この位相を用い、2つ目の重原子誘導体KHgI<sub>4</sub>-Kの5カ所の水銀結合部位を求めた。K<sub>2</sub>PtCl<sub>4</sub>、KHgI<sub>4</sub>-K両方の重原子パラメーターをMLPHAREを用いて同時に精密化した後、プログラムDMを用いて、溶媒平滑化とヒストグラムマッピングを行い、位相を改良した。ちなみに、K<sub>2</sub>PtCl<sub>4</sub>については異常分散データも使用した。この良好な位相を用いて計算した電子密度マップは非常に鮮明で、ほとんどのアミノ酸残基をきれいにフィットすることができた。最初のモデルは、2.8Å分解能で作成した電子密度マップ上でプログラムQUANTAを用いて構築し、プログラムX-PLORを用いて構造精密化を行った。N末の6残基、135-136番目の残基、C末の1残基は電子密度が観測されず、構造を一義的に決定できな



った。1.9 Å分解能で精密化された最終モデル(図4～図6)は、全231残基中222残基、236個の水分子、1分子の硫酸イオンを含む。硫酸イオンは、精製過程で用いた硫酸アンモニウムに由来しており、活性中心のリン酸結合部位に一致するものと考えられる。8～1.9 Å分解能の反射を用いた結晶学的信頼度因子(R因子)は21.5%となった。平均の温度因子は、蛋白質原子について $2.6 \text{ Å}^2$ 、水分子について $4.5 \text{ Å}^2$ となった。プログラムPROCHECKを用いてラマチャンドラプロットを作成したところ、グリシン以外の残基の93%が最も好ましい領域に、7%が次に好ましい領域に位置することが示された。非対称単位にはサブユニット1個が含まれ、結晶学的対称性によって6量体が形成される。原子座標は図10～図45に示した。

【0022】なお、図4は、EB-A Pの6量体分子の結晶構造を示すCG写真である。 $\alpha$ 炭素原子の流れをリボンモデルで表示した。また、活性中心をマークする硫酸イオンをボールモデルで表示した。図5は、EB-A Pのサブユニットの結晶構造を示すCG写真である。 $\alpha$ 炭素原子の流れをリボンモデルで表示した。また、活性中心をマークする硫酸イオンをボールモデルで表示した。図6は、EB-A Pの活性部位構造を示す図である。中央に硫酸イオンを示した。また、水素結合を点線で示した。図10は、EB-A Pの構造の結晶学データ(1)を示す図である。図11は、EB-A Pの構造の結晶学データ(2)を示す図である。図12は、EB-A Pの構造の結晶学データ(3)を示す図である。図13は、EB-A Pの構造の結晶学データ(4)を示す図である。図14は、EB-A Pの構造の結晶学データ(5)を示す図である。図15は、EB-A Pの構造の結晶学データ(6)を示す図である。図16は、EB-A Pの構造の結晶学データ(7)を示す図である。図17は、EB-A Pの構造の結晶学データ(8)を示す図である。図18は、EB-A Pの構造の結晶学データ(9)を示す図である。図19は、EB-A Pの構造の結晶学データ(10)を示す図である。図20は、EB-A Pの構造の結晶学データ(11)を示す図である。図21は、EB-A Pの構造の結晶学データ(12)を示す図である。図22は、EB-A Pの構造の結晶学データ(13)を示す図である。図23は、EB-A Pの構造の結晶学データ(14)を示す図である。図24は、EB-A Pの構造の結晶学データ(15)を示す図である。図25は、EB-A Pの構造の結晶学データ(16)を示す図である。図26は、EB-A Pの構造の結晶学データ(17)を示す図である。図27は、EB-A Pの構造の結晶学データ(18)を示す図である。図28は、EB-A Pの構造の結晶学データ(19)を示す図である。図29は、EB-A Pの構造の結晶学データ(20)を示す図である。図30は、EB-A Pの構造の結晶学データ(21)を示す図である。図

31は、EB-A Pの構造の結晶学データ(22)を示す図である。図32は、EB-A Pの構造の結晶学データ(23)を示す図である。図33は、EB-A Pの構造の結晶学データ(24)を示す図である。図34は、EB-A Pの構造の結晶学データ(25)を示す図である。図35は、EB-A Pの構造の結晶学データ(26)を示す図である。図36は、EB-A Pの構造の結晶学データ(27)を示す図である。図37は、EB-A Pの構造の結晶学データ(28)を示す図である。図38は、EB-A Pの構造の結晶学データ(29)を示す図である。図39は、EB-A Pの構造の結晶学データ(30)を示す図である。図40は、EB-A Pの構造の結晶学データ(31)を示す図である。図41は、EB-A Pの構造の結晶学データ(32)を示す図である。図42は、EB-A Pの構造の結晶学データ(33)を示す図である。図43は、EB-A Pの構造の結晶学データ(34)を示す図である。図44は、EB-A Pの構造の結晶学データ(35)を示す図である。図45は、EB-A Pの構造の結晶学データ(36)を示す図である。

【0023】実施例5 野生型EB-A Pと5'-イノシンの結合様式モデルの推測  
イノシンのEB-A Pに対する $K_m$ 値は100 mMを超えることから、結合様式をX線結晶構造解析で決定できるほど親和性が高くない。実際に、グルコース-6-サルフェートやアデノシン-チオモノホスフェートといったEB-A Pの阻害剤となる化合物を野生型EB-A Pの結晶にソーキングした後、X線回折データを収集し、電子密度マップを作成したが、これら化合物に対応する電子密度は観測されなかった。そこで、コンピュータグラフィックスを用いて、5'-イノシン酸とEB-A Pの結合様式の推測(いわゆる、ドッキングスタディ)を行うこととした。プログラムはQUANTAを用いた。結晶構造中、活性部位中央に硫酸イオンが見出されたので、ここに、5'-イノシン酸のリン酸基を重ね合せた。更に、G74D及びI153Tの変異が5'-イノシン酸のEB-A Pに対する $K_m$ 値を低下させることが知られていたため、5'-イノシン酸はG74及びI153から遠くないところに結合すると判断し、5'-イノシン酸の位置を決めた。その際、5'-イノシン酸を構成する原子とEB-A Pを構成する原子がお互いにぶつからないようにした。こうして構築したモデルにおいて、I153がTになると、置換されたスレオニンの側鎖の $\gamma$ 酸素原子とイノシンのリボースの2'水酸基が水素結合を形成する。また、プログラムGRASPを用いてEB-A Pの静電ポテンシャル表示をしたところ、正電荷を帯びるイノシン塩基は、EB-A P分子表面で負電荷を帯びている領域と相互作用しており、モデルがもっともらしいことが示唆された。

【0024】実施例6 G74D/I153T変異型E



### B-A Pの結晶構造解析

G74D/I153T変異型E-B-A Pは、ホスファターゼ活性に対するリン酸基転移活性の比率が高まっており、それに伴い、ヌクレオシド-5'-リン酸の生産能力も向上している。これは、ヌクレオシドとのKm値が低下したこと、すなわち、ヌクレオシドとの親和性が向上したことが原因として考えられている。この変異型E-B-A Pの結晶構造を決定し、野生型E-B-A Pの結晶構造と比較すれば、ヌクレオシドとの親和性向上の分子機構が解明されることを期待した。常温で、最高2.4 Å分解能データまでのX線回折データを測定した。単位格子の体積、空間群、酵素の分子量から見積もって、非対称単位には6量体の分子1つが含まれることが予想された。そこで、野生型E-B-A Pの6量体構造を探索モデルとして、プログラムamoreを用いて分子置換法により解析を行った。rotation searchにおいては1.0~3 Å分解能のデータを、translation searchにおいては1.0~4 Å分解能のデータを用いた。両サーチともに、正解がトップピークとして現れた。分子を剛体として精密化を行ったところ、R因子は37.3%に低下した。この後、QUANTAを用いたグラフィックス上での構造修正とX-PLORを用いた構造精密化を繰り返し行い、1.0~2.4 Å分解能において、R因子19.9%のモデルを得た。実施例5と同様の方法で、5'-イノシン酸とG74D/I153T変異型E-B-A Pの結合モデルを作成したところ、置換されたThr153の側鎖のγ酸素原子は、イノシンのリボースの水酸基と水素結合を形成することが予想された。また、もう一つ置換が施されたAsp74を含むループの揺らぎが、野生型に比べG74D/I153T変異型E-B-A Pの方が大きくなっていることが、温度因子を比較することにより分かった。このループはイノシンの塩基と相互作用することが予想されるが、揺らぎが大きくなったことにより塩基との結合がしやすくなった可能性が示唆される。

【0025】実施例7 野生型E-B-A Pとモリブデン酸との複合体（反応中間体アナログ）の結晶構造解析 E-B-A Pの酵素反応において、まず初めに、リン酸モノエステル結合が切断され、リン酸基は活性残基のHis189と共有結合を形成する。この状態の酵素分子を反応中間体と呼ぶ。反応中間体は速やかに、水あるいはアルコールによるアタックを受け、その結果、リン酸イオンが離脱する。水がアタックすればホスファターゼ活性が発揮されることとなり、また、アルコールがアタックすればリン酸基転移活性が発揮されることになる。いずれにしても、反応中間体は不安定であり、その構造をX線結晶構造解析により決定することは不可能である。しかし、リン酸の代わりにモリブデン酸がHis189に共有結合したもの（反応中間体アナログ）は、水によるアタックを受けないので安定に存在する。リン酸基転移反応においては、反応中間体にリン酸受容体が結合し、リ

ン酸モノエステル結合が形成される。したがって、ヌクレオシドとの結合様式を推定する目的においては、遊離型構造よりも、反応中間体構造を用いる方が適切である。反応中間体とヌクレオシドとのドッキングスタディを行う目的で、反応中間体アナログの結晶構造解析を行った。常温にて、最高2.4 Å分解能データまでのX線回折データを測定した。単位格子の体積、空間群、酵素の分子量から見積もって、非対称単位には6量体の半分、すなわち、サブユニット3つが含まれることが予想された。そこで、3回軸によってお互いが関係づけられる3量体構造を作成し、分子置換法の探索モデルとした。rotation searchにおいては1.0~3 Å分解能のデータを、translation searchにおいては1.0~4 Å分解能のデータを用いた。両サーチともに、正解がトップピークとして現れた。分子を剛体として精密化を行ったところ、R因子は42.4%に低下した。この後、QUANTAを用いたグラフィックス上での構造修正とX-PLORを用いた構造精密化を繰り返し行い、8~2.4 Å分解能において、R因子22.3%のモデルを得た。非対称単位には6量体の分子半分、つまりサブユニット3つが含まれる。

### 【0026】実施例8 E-B-A P反応中間体とイノシンの結合様式モデルの推測

コンピュータグラフィックス上、QUANTAを用いて、結合様式モデルを構築した（図3）。モリブデン酸はそのままリン酸に置き換えた。イノシンは、野生型E-B-A Pと5'-イノシン酸の結合様式モデルにおける5'-イノシン酸のヌクレオシド部分近くに置いた。ただし、当然のことだが、イノシンはリン酸モノエステル結合を持たないので、5'-イノシン酸をドッキングさせるよりも自由度が高い。したがって、イノシンがE-B-A Pの分子表面に、より好ましい状態で結合するように、イノシンの位置の微調整を行い、結合様式モデルとした。以降の変異型酵素のデザインには、このモデルを用いることとした。

### 【0027】実施例9 ヌクレオシドとの親和性向上を目指した変異型E-B-A Pのデザイン

実施例8で構築したモデルによると、Ser72の側鎖は、イノシンの塩基と相互作用する可能性が示唆された。この残基をフェニルアラニン、チロシン、トリプトファンといった芳香族アミノ酸に置換すると、芳香環とヌクレオシド塩基との間にπ-π相互作用が生じ、ヌクレオシドのE-B-A Pに対する親和性が向上することが予測された。同様に、バリン、ロイシン、イソロイシンといった分岐鎖疎水性アミノ酸に置換すると、分岐鎖疎水基とヌクレオシド塩基との間にC-H/π相互作用が生じ、また、グルタミン酸、アスパラギン酸といった負電荷を帯びたアミノ酸に置換すると、ヌクレオシド塩基の正電荷と静電的に引き合い、親和性の向上が見込まれた。そこで、ホスファターゼ活性よりもリン酸基転移活

性が相対的に高まっているG74D/I153T変異型EB-A Pのリン酸基転移活性を更に高めるため、該変異型EB-A PのS72F, S72Y, S72W, S72V, S72E, S72D変異体を作製することとした。なお、S72を他のアミノ酸に置換した変異体も作製することとした。ちなみに、これら変異体は、3残基置換変異型EB-A Pとなる。

【0028】実施例10 Ser72を他のアミノ酸へ置換した3残基置換変異型EB-A Pの作製  
エシェリヒア・コリJM109で発現するための9種類の変異型EB-A Pを構築するために、G74D/I153T変異型EB-A P遺伝子を含むプラスミドpEPI340を、PCRを用いる部位特異的突然変異誘発法の鋳型として使用した。なお、pEPI340は、プラスミドpEPI305にG74D/I153Tの変異を加えたプラスミドである。しかして、これらプラスミドpEPI305及びpEPI340の塩基配列は、特開平10-201481号公報の段落番号(0143)の表12に明記されている。また、プラスミドpEPI305をエシェリヒア・コリJM109に保持させた株は、AJ13144と命名され、通商産業省工業技術院生命工学工業技術研究所にFERM BP-5423として国際寄託されている〔上記公開公報の段落番号(0105)～(0110)の記載参照〕。変異はストラタジーン(Stratagene)社(アメリカ)の「クイックチェンジ部位特異的突然変異誘発キット(Quickchange Site-Directed Mutagenesis Kit)」を使用し、製造元のプロトコールに従って、各種変異型酵素に対応するプライマー(図7、配列表の配列番号11～61)を用いて導入した。PCR反応の生成物を用いて、エシェリヒア・コリXL-1を形質転換した。形質転換細胞を、100 $\mu$ l/mlのアンピシリンを含むL寒天培地プレート上に塗抹し、37℃で16時間インキュベートした。生成したコロニーを採取し、100 $\mu$ l/mlのアンピシリンを含むL培地で一晩振とうしながら培養した。培養液から遠心分離により菌体を回収後、ファルマシア社(スウェーデン)のFlexiPrep Kitを使用し、製造元のプロトコールに従って、プラスミドの抽出を行った。各種3残基置換変異型EB-A Pをコ

ードする塩基配列は、DNA配列分析によって確認した。なお、図7に示したプライマーセットの合成は(株)日本バイオサービスに委託した。

【0029】実施例11 変異型EB-A Pのリン酸基転移活性及び反応速度定数の測定

各種3残基置換変異型EB-A P遺伝子を含むプラスミドを導入したエシェリヒア・コリJM109を100 $\mu$ l/mlのアンピシリンを含むL培地50mlに接種し、37℃で16時間培養した。培養液から遠心分離で菌体を集め、25mMリン酸バッファー(pH7.0)3mlに懸濁し、4℃で20分間超音波処理を行い破碎した。処理液を遠心分離して不溶性画分を除き、無細胞抽出液を調製した。各EB-A P3残基置換変異型酵素が発現していることは、SDS-PAGEで確認した。発現量は、全蛋白質の20%程度であった。無細胞抽出液のリン酸基転移活性は以下の条件で測定した。2mMイノシン、100mMピロリン酸ナトリウム、100mM酢酸バッファー(pH4.0)、100 $\mu$ lの無細胞抽出液を含む反応液(1ml)を、pH4、30℃で10分間インキュベートした。1N塩酸200 $\mu$ lを加え反応を停止させた後、遠心分離により沈殿を除き、生成した5'-イノシン酸を定量した。各種3残基置換変異型EB-A Pのリン酸基転移活性を、変異を導入する対象としたG74D/I153T変異型EB-A Pを用いたときの5'-イノシン酸生成量を1とした相対活性で示した。続いて、各種3残基置換変異型EB-A Pのリン酸基転移反応におけるイノシンに対するKm値を以下の条件で測定した。100mMピロリン酸ナトリウム、100mM酢酸バッファー(pH4.0)、10-100mMイノシン、100 $\mu$ lの無細胞抽出液を含む反応液(1ml)をpH4、30℃で10分間インキュベートした。1N塩酸200 $\mu$ lを加え反応を停止させた後、遠心分離により沈殿を除き、生成した5'-イノシン酸を定量した。Hanes-WoolfプロットによりKm値を算出した。表2に結果を示す。

【0030】

【表2】

	Km値	リン酸転移活性
S72F/G74D/I153T	20mM	2.80
S72Y/G74D/I153T	25mM	2.04
S72W/G74D/I153T	30mM	1.71
S72D/G74D/I153T	33mM	1.59
S72V/G74D/I153T	40mM	2.46
S72E/G74D/I153T	40mM	3.19
S72M/G74D/I153T	46mM	1.94
S72T/G74D/I153T	50mM	1.91
S72L/G74D/I153T	57mM	2.24
S72R/G74D/I153T	59mM	1.99
S72Q/G74D/I153T	77mM	2.42
S72K/G74D/I153T	78mM	1.53
S72P/G74D/I153T	109mM	1.34
S72A/G74D/I153T	115mM	0.78
S72N/G74D/I153T	124mM	0.43
S72G/G74D/I153T	137mM	0.43
S72H/G74D/I153T	n. d.	n. d.
G74D/I153T	100mM	1.00
10残基置換変異型	40mM	1.44

【0031】実施例9にて、 $\pi$ - $\pi$ 相互作用、CH/ $\pi$ 相互作用、静電相互作用によりイノシンとの親和性が向上するであろうと予測されたすべての変異体(S72F, S72Y, S72W, S72V, S72L, S72E, S72D)のイノシンに対するKm値が、変異導入しないG74D/I153T変異型EB-APのものに比べて低下し、イノシンに対する親和性が向上した。また、リン酸基転移活性についても向上が見られた。特に、S72Fを導入した変異体が、Km値、リン酸基転移活性、双方において、改善が著しかった。フェニルアラニンの芳香環とイノシン塩基が適当な位置関係で $\pi$ - $\pi$ 相互作用し、親和性の向上が図られたものと推測される。また、S72M, S72T, S72R, S72Q, S72K変異体のKm値も低下した。これらアミノ酸残基とヌクレオシド塩基の間に疎水性相互作用、水素結合等何らかの好ましい相互作用が生じたものと考えられる。ちなみに、S72Iについては、遺伝子を作製できなかった。また、S72Cは、誤ったS-S結合を形成させる危険性があるので、作製しなかった。なお、5'-イノシン酸は、高速液体クロマトグラフィー(HPLC)により、下記の条件にて分析した。

カラム: Cosmosil 5C18-AR (4.6×150mm)

ナカライテスク社製品

移動相: 5mM リン酸カリウムバッファー(pH2.8)/メタノール=95/5

流速: 1.0ml/min

温度: 室温

検出: UV245nm

【0032】実施例12 S72F/G74D/I153T

3T変異型EB-AP遺伝子を導入したエシェリヒア・コリJM109を用いた5'-イノシン酸の生産  
G74D/I153T変異型、10残基置換変異型、及びS72F/G74D/I153T変異型EB-AP遺伝子を含むプラスミドを導入したエシェリヒア・コリJM109をアンピシリン100 $\mu$ g/ml及びIPTG 1mMを含むL培地50mlに接種し、37℃で16時間培養した。ピロリン酸12g/dl、及びイノシン6g/dlを酢酸バッファー(pH4.0)に溶解し、これに上記の各変異型EB-AP遺伝子を導入したエシェリヒア・コリJM109の菌体を乾燥菌体重量で100mg/dlとなるように添加し、pHを4.0に維持しながら、30℃で24時間反応を行った。生成した5'-イノシン酸の量を測定した結果を表3に示した。なお、生成したイノシン酸は5'-イノシン酸のみで2'-イノシン酸及び3'-イノシン酸の副生は全く認められなかった。G74D/I153T変異型EB-AP遺伝子を含むプラスミドを導入したエシェリヒア・コリJM109を用いた反応では7.5g/dlの5'-イノシン酸が生成蓄積したが、反応時間を伸ばしてもそれ以上蓄積は増加しなかった。10残基置換変異型EB-AP遺伝子を含むプラスミドを導入したエシェリヒア・コリJM109を用いた反応では蓄積が向上し、12.1g/dlの5'-イノシン酸が生成蓄積した。立体構造に基づいて設計し、構築したS72F/G74D/I153T変異型EB-AP遺伝子を含むプラスミドを導入したエシェリヒア・コリJM109を用いた反応では更に生産性が向上し、13.2g/dlの5'-イノシン酸が生成蓄積した。

【0033】

【表3】

導入した変異型酵素遺伝子	生成イノシン酸(g/dl)
G74D/I153T	7.5
10残基置換変異型	12.1
S72F/G74D/I153T	13.2

【0034】実施例13 L16W, S71W, S73W, E104F, E104W変異を導入した3残基置換変異型E-B-A-Pのリン酸基転移活性及び反応速度定数の測定

S72F変異が、 $\pi$ - $\pi$ 相互作用によりイノシンとの親和性を向上させたと考えられるため、コンピューターグラフィックス上で、芳香環アミノ酸への置換によりイノシン塩基との $\pi$ - $\pi$ 相互作用が図れる他のアミノ酸残基を探索した。その結果、L16W, S71W, S73W, E104F, E104W変異により置換された芳香環がイノシン塩基と相互作用する可能性が示唆された。そこで、これら5種の(G74D/I153T変異型E-B-A-Pをベースとした)3残基置換変異型E-B-A-Pを実施例10に記述した方法(各変異型酵素に対応するプライマーは図8に示した。配列表の配列番号62~76)で作製し、実施例11に記述した方法でリン酸基転移活性及び反応速度定数を測定した。結果を表4に示す。リン酸基転移活性はいずれの変異型酵素においても低下したが、Km値はすべての変異型酵素で低下し、イノシンとの親和性が向上したことが示唆された。Leu16は、イノシンとの相互作用が確実視されるSer72から(C $\alpha$ 間距離で)10Å離れているが、この程度離れていてもイノシンとの相互作用が可能であることが示された。なお、図8に示したプライマーセットの合成は、(株)日本バイオサービスに委託した。

【0035】

【表4】

	Km値	リン酸基転移活性
L16W/G74D/I153T	33mM	0.21
S71W/G74D/I153T	75mM	0.26
S73W/G74D/I153T	29mM	0.77
E104F/G74D/I153T	61mM	0.65
E104W/G74D/I153T	67mM	0.26
G74D/I153T	100mM	1.00
10残基置換変異型酵素	40mM	1.44

【0036】実施例14 エンテロバクター・アエロゲネス(Enterobacter aerogenes)由来酸性ホスファターゼ(E-A-P)の変異型酵素遺伝子の作製と該遺伝子を導入したエシェリヒア・コリJM109を用いた5'-イノシン酸の生産

E-B-A-Pにおいてイノシンのリン酸基転移活性を向上させたS72F/G74D/I153Tの3つの変異に相同な変異をE-A-Pに導入することとした。E-B-A-PとE-A-Pのアミノ酸配列をプログラムBLASTを用いて、アラインメントした結果を図9に示す。E-B-A-PのSer72/Gly74/Ile153は、E-A-Pにおいては、Ala70/Gly72/Ile151に対応するこ

とが示された。そこで、A70F/G72D/I151T変異型E-A-Pを実施例10に記述した方法で作製した。変異型酵素遺伝子を含むプラスミドを導入したエシェリヒア・コリJM109を用いて、イノシンから5'-イノシン酸の生産を実施例12に記述した方法で行った。結果を表5に示す。A70F/G72D/I151T変異型E-A-Pは、S72F/G74D/I153T変異型E-B-A-Pと同等の5'-イノシン酸生産能を示した。

【0037】

【表5】

導入した変異型酵素遺伝子	生成イノシン酸(g/dl)
EA-AP A72F/G74D/I153T	13.1
EB-AP S72F/G74D/I153T	13.2

【0038】なお、図9はEB-APとエンテロバクター・アエロゲネス由来酸性ホスファターゼ(EA-AP)のアミノ酸配列アラインメントをプログラムBLASTにより行った結果を示す図である。上段がEB-AP、下段がEA-APである。中段には、両者のアミノ酸残基が同一であればその残基名が、同一でなくても類似のアミノ酸残基であれば、+が表示される。EB-APの72番目の残基(Ser72)の位置を、[72]でマークした。EA-APで対応する残基はAla70である。

【0039】実施例15 モルガネラ・モルガニ由来酸性ホスファターゼ(MM-AP)由来G72D/I151T変異型酵素の結晶化及び結晶構造解析

ハンギングドロップ法での蒸気拡散を利用してMM-APのG72D/I151T二重変異体の結晶化を行った。当該蛋白質溶液(濃度40mg/ml)と、25(w/v%)のポリエチレングリコール1000、25mM 硫酸、25mM DTTを含む125mM クエン酸緩衝液(pH4.8)を同量ずつ(各々5 $\mu$ l)、シリコナイゼーションしたカバーガラス上に滴下混合し、25(w/v%)のポリエチレングリコール1000、25mM 硫酸、25mM DTTを含む125mM クエン酸緩衝液(pH4.8)50 $\mu$ lを満たしたウェルの上に混合液滴が釣り下がるようにかぶせ、20℃にて静置した。2、3日後に結晶が析出し、1週間後には測定可能な大きさ(0.4 $\times$ 0.4 $\times$ 0.3mm程度)に成長した。(株)リガクのX線回折装置R-Axis IIcを用いて、X線回折データを収集し、結晶学的パラメーターを決定した。空間群はP2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>、格子定数はa=90.64Å、b=119.74Å、c=136.14Åとなった。筑波・高エネルギー研究所シンクロトロン放射光施設BL-6B上、100Kで、2.6Å分解能データまでの回折データを測定した。単位格子の体積、空間群、酵素の分子量から見積もって、非対称単位には6量体の分子1つが含まれることが予想された。そこで、野生型EB-APの6量体構造を探索モデルとして、プログラムamoreを用いて分子置換法により解析を行った。rotation searchにおいては10~3Å分解能のデータを、translation searchにおいては10~4Å分解能のデータを用いた。両サーチともに、正解がトップピークとして現れた。分子を剛体として精密化を行った後、QUANTAを用いたグラフィックス上での構造修正とX-PLORを用いた構造精密化を繰り返して、10~2.6Å分解能において、R因子0.197のモデルを得た。図1に示した5つの活性残基(Lys113、Arg120、His148、Arg181、H

is187)のC $\alpha$ 原子間の距離を表6に示した。EB-APの類縁酵素であるMM-APにおいて、活性残基間のすべての原子間距離が、EB-APの立体構造から規定した範囲におさまっていることが確認された。

【0040】

【表6】

		G74D/I153T 変異型MM-AP	下限	上限
Lys113	Arg120	11.3Å	10.4Å	12.6Å
	His148	12.6Å	11.3Å	13.8Å
	Arg181	16.3Å	14.5Å	17.4Å
	His187	12.5Å	10.7Å	13.6Å
Arg120	His148	14.0Å	12.2Å	15.2Å
	Arg181	10.9Å	9.4Å	11.8Å
	His187	6.1Å	4.5Å	6.7Å
His148	Arg181	8.9Å	6.7Å	9.8Å
	His187	10.2Å	8.8Å	11.0Å
Arg181	His187	5.4Å	4.5Å	6.8Å

【0041】実施例16 A72F、A72E変異を導入した10残基置換変異型EB-APの作製、及びリン酸転移活性と反応速度定数の測定

実施例11において、最もKm値を低下させたS72Fと最も活性を高めたS72E変異を、10残基置換変異型EB-APに導入した。10残基置換変異型EB-APにおいては、Ser72がAlaに置換されているので、実際には、A72FとA72E変異を導入することとなる。野生型EB-APを基準とすると、双方とも10残基が置換されている。これら2種の変異体を実施例10に記述した方法(各変異型酵素に対応するプライマーは図46に示した。配列表の配列番号77~82)で作製した。PCRを用いる部位特異的突然変異誘発法の鋳型としては、10残基置換変異型EB-AP遺伝子を含むプラスミドpEMP370(特開平9-37785号公報、実施例19)を使用した。更に、実施例11に記述した方法でリン酸転移活性及び反応速度定数を測定した。結果を表7に示す。リン酸転移活性は、G74D/I153T変異型EB-APを用いたときの5'-イノシン酸生成量を1とした相対活性で示した。いずれの変異型酵素においても、Km値は顕著に低下した。リン酸転移活性については、A72F変異により低下したのに対し、A72E変異により上昇した。

【0042】

【表7】

	Km値	リン酸転移活性
A72F/10残基置換変異型酵素	9mM	0.11
A72E/10残基置換変異型酵素	15mM	2.30
10残基置換変異型酵素	40mM	1.44

【0043】実施例17 A72F/10残基置換変異型EB-AP及びA72E/10残基置換変異型遺伝子を導入したエシェリヒア・コリJ M109を用いた5'-

イノシン酸の生産

A72F/10残基置換変異型EB-AP及びA72E/10残基置換変異型遺伝子を含むプラスミドを導入し

たエシェリヒア・コリJM109を用いての5'-イノシン酸の生産実験を実施例12に記述した方法で行った。結果を表8に示す。両変異体とも5'-イノシン酸の蓄

積量が増加した。

【0044】

【表8】

導入した変異型酵素遺伝子	生成イノシン酸(g/dl)
A72F/10残基置換変異型	13.9
A72E/10残基置換変異型	13.9
10残基置換変異型	12.1

【0045】実施例18 I103D、T153N変異を導入した変異型EB-APの作製、及びリン酸転移活性及び反応速度定数の測定

I103D変異により、置換されたAspがイノシン塩基と静電相互作用をすること、また、T153N変異により、置換されたAsnがリボースの水酸基と水素結合を形成することが図3のモデルにより示唆された。そこで、G74D/I153T変異型EB-APにこれらの残基を導入し、I103D/G74D/I153T変異型EB-APとG74D/I153N変異型EB-APを実施例10に記述した方法（各変異型酵素に対応する

プライマーは図47に示した。配列表の配列番号83～88）で作製することとした。更に、実施例11に記述した方法でリン酸転移活性及び反応速度定数を測定した。結果を表9に示す。リン酸転移活性は、G74D/I153T変異型EB-APを用いたときの5'-イノシン酸生成量を1とした相対活性で示した。両変異体ともに、リン酸基転移活性は低下したが、Km値は低下し、イノシンとの親和性が向上したことが示唆された。

【0046】

【表9】

	Km値	リン酸転移活性
I103D/G74D/I153T	51mM	0.09
G74D/I153N	38mM	0.18
G74D/I153T	100mM	1.00

【0047】実施例19 Leu140をPhe、Glu、Lysに置換した変異型EB-APの作製、及びリン酸転移活性と反応速度定数の測定

Leu140は、Ser72から10Å以上離れているが、反応中間体アナログの立体構造において、リン酸結合部位の直近に位置する。したがって、この残基を置換すれば、反応中間体におけるリン酸結合部位周辺の構造が変化し、ひいては、ヌクレオシド結合部位の構造と揺らぎにも影響が及ぶものと考えられた。この残基を、よりかさ高いPhe、正電荷を有するLys、負電荷を有するGlu、に置換すれば、ヌクレオシドとの親和性が変化するのではないかと期待される。変異は、実施例16においてリン酸転移活性が高かったA72E/10残基置換体

に導入することとした。これら3種の変異体を実施例10に記述した方法（各変異型酵素に対応するプライマーは図48に示した。配列表の配列番号89～97）で作製した。PCRを用いる部位特異的突然変異誘発法の鑄型としては、A72E/10残基置換変異型EB-AP遺伝子を含むプラスミドを使用した。更に、実施例11に記述した方法でリン酸転移活性及び反応速度定数を測定した。結果を表10に示す。リン酸転移活性は、G74D/I153T変異型EB-APを用いたときの5'-イノシン酸生成量を1とした相対活性で示した。

【0048】

【表10】

	Km値	リン酸転移活性
A72E/L140F/10残基置換変異型酵素	9mM	1.66
A72E/L140K/10残基置換変異型酵素	78mM	0.07
A72E/L140E/10残基置換変異型酵素	322mM	0.16
A72E/10残基置換変異型酵素	15mM	2.30

【0049】L140Fを導入した変異体は、Km値が低下した。逆に、L140K及びL140E変異は、Kmを大幅に上昇させた。

【0050】実施例20 エンテロバクター・アエロゲネス IF012010 由来野生型酸性ホスファターゼの精製とN末端アミノ酸配列の決定

特開平10-201481号公報の実施例24記載のエシェリヒア

・コリJM109/pENP110の培養菌体からエンテロバクター・アエロゲネス IF012010由来の酸性ホスファターゼを精製してN末端アミノ酸配列を決定し、成熟蛋白質のアミノ酸配列を決定した。エシェリヒア・コリ JM109/pENP110はエンテロバクター・アエロゲネス IF012010由来の酸性ホスファターゼ遺伝子を実験例11に記述した方法で導入した菌で、該酸性ホスファターゼを生産する。該

酸性ホスファターゼ遺伝子の塩基配列より予想される前駆体蛋白質のアミノ酸配列は配列表の配列番号 10 に示される配列である。ペプトン 1 g/dl、酵母エキス 0.5 g/dl 及び食塩 1 g/dl を含有する栄養培地 (pH7.0) 50 ml を 500 ml 坂口フラスコに入れ、120℃にて20分間加熱殺菌した。これにエシェリヒア・コリ JM109/pENP110を一白金耳接種し、30℃で16時間振とう培養した。培養液から遠心分離により菌体を回収した菌体を100 ml の100mMリン酸カリウムバッファー (pH7.0) に懸濁し、4℃で20分間超音波処理を行い菌体を破碎した。処理液を遠心分離して不溶性画分を除き、無細胞抽出液を調製した。この無細胞抽出液に30%飽和となるように硫酸アンモニウムを添加した。遠心分離により生成した沈殿を除去した後、上清液に60%飽和となるように硫酸アンモニウムを追加添加した。生成した沈殿を遠心分離により回収し、100mMリン酸カリウムバッファーに溶解した。この粗酵素液を100mMリン酸カリウムバッファー (pH7.0) 500ml に対し3回透析した後、20mMリン酸カリウムバッファー (pH7.0) で平衡化したDEAE-トヨパール650Mカラム ( $\phi$  3.0×10.0cm) にチャージし、20mMリン酸カリウムバッファー (pH7.0) で洗浄した。リン酸転移活性は素通り画分にあったので、当該画分を回収した。この活性画分に35%飽和となるように硫酸アンモニウムを添加し、これを35%飽和硫酸アンモニウムを含む20mMリン酸カリウムバッファー (pH7.0) で平衡化したブチルトヨパールカラム ( $\phi$  3.0×7.0cm) に吸着させた。これを35%飽和から20%飽和リン酸カリウムバッファー (pH7.0) の直線的な濃度勾配で溶出した。活性画分を集め、10mMリン酸カリウムバッファー (pH6.0) 1 L に対し透析した後、10mMリン酸カリウムバッファー (pH6.0) で平衡化したCM-トヨパールカラム ( $\phi$  3.0×7.0cm) に吸着させた。これを0mMから300mM 塩化カリウムを含むリン酸カリウムバッファー (pH6.0) の直線的な濃度勾配で溶出した。この活性画分を集めた。以上の操作によって、リン酸転移活性を示す酵素を無細胞抽出液より最終的に約16%の回収率で約5倍に精製した。この酵素標品は、SDS-ポリアクリルアミド電気泳動において均一であった。本精製酵素をDITCメンブレン〔ミリゲン/バイオサーチ (Milligen/Biosearch) 社製〕に吸着させ、Prosequencer 6625 (ミリゲン/バイオサーチ社製) を用いてN末端のアミノ酸配列を決定したところ配列表の配列番号 98 に示した5残基のN末端のアミノ酸配列が決定された。精製酵素のN末端は配列表の配列番号 10 の配列の21番目のアラニン残基から開始していたため、配列表の配列番号 10 に示されるアミノ酸配列は前駆体蛋白質の配列であり、1番目のメチオニン残基から20番目のフェニルアラニン残基までのペプチドは翻訳後に除去されるものと考えられた。この結果より成熟体蛋白質のアミノ酸配列は配列表の配列番号 10 に示される配列中、アミノ酸番号 1~228 に示される配列であると考

えられた。

【0051】実施例 21 エンテロバクター・アエロゲネス IF0 12010 由来新規変異型酸性ホスファターゼ遺伝子のプロモーター配列の改変による酵素の高発現  
エンテロバクター・アエロゲネス IF0 12010由来変異型酸性ホスファターゼをコードする遺伝子のプロモーター配列部分に遺伝子工学的手法によって部位特異的変異を導入し、酵素発現量の増加した変異型酸性ホスファターゼをコードする遺伝子を構築した。変異を導入する遺伝子は特願平12-189226号明細書の実施例3にて構築したプラスミド pENP170 を用いた。本プラスミドはエンテロバクター・アエロゲネス IF0 12010由来変異型酸性ホスファターゼをコードする遺伝子を含む制限酵素 S a l I と制限酵素 K p n I で切り出される1.6 kbp DNA断片を、S a l I 及び K p n I で切断した pUC19 (宝酒造社製) に連結したプラスミド DNA であり、pENP170 中の S a l I - K p n I 1.6 kbp DNA断片の塩基配列は配列表の配列番号 9 に示される配列である。プラスミド DNA への変異導入はストラタジーン社製のクイックチェンジ部位特異的突然変異誘発キット (Quick Change site-directed mutagenesis kit) を用いた。DNA 合成装置 (アプライドバイオシステム社製モデル394) を用いて合成した変異導入用オリゴヌクレオチド MUT170 (配列表の配列番号 99)、MUT171 (配列表の配列番号 100)、及び鋳型として pENP170 を用いてストラタジーン社のプロトコールに従って変異を導入した。得られたプラスミド DNA を用いて常法によりエシェリヒア・コリ JM109 (宝酒造社製) を形質転換した。これを 100  $\mu$ g/ml のアンピシリンを含む L 寒地培地上にプレーティングし、形質転換体を得た。形質転換体よりアルカリ溶菌法によりプラスミドを調製し、塩基配列の決定を行い、目的の塩基が置換されていることを確認した。塩基配列の決定は Taq DyeDeoxy Terminator Cycle Sequencing Kit (アプライドバイオケミカル社製) を用い、サンガーの方法〔ジャーナル オブ モレキュラー バイオロジー (J. Mol. Biol.)、第143巻、第161頁 (1980)〕に従って行った。このようにしてエンテロバクター・アエロゲネス IF0 12010由来推定酸性ホスファターゼの上流に位置する推定プロモーター配列の -10 領域の塩基配列が AAAAAT からエシェリヒア・コリの lac プロモーターと同じ TATAAT という塩基配列に変異した変異型遺伝子をコードする変異型遺伝子を構築した。この変異型遺伝子を含むプラスミドを pENP180 と命名した。

【0052】エシェリヒア・コリ JM109/pENP170 及びプロモーター配列の -10 領域を改変した遺伝子を導入したエシェリヒア・コリ JM109/pENP180 をアンピシリン 100  $\mu$ g/ml を含む L 培地 50 ml、及び IPTG 1 mM を添加したアンピシリン 100  $\mu$ g/ml を含む L 培地 50 ml にそれぞれ接種し、37℃で16時間培養した。それぞれの菌の培養液から遠心分離により菌体を集め、生理食塩水

で1回洗浄した。ピロリン酸15g/dl、及びイノシン、8g/dlを100mM酢酸バッファー (pH4.0) に溶解し、これにそれぞれの菌体を乾燥菌体重量で100mg/dlとなるように添加し、pHを4.0に維持しながら、30℃で1時間反応させた。生成した5'-イノシン酸の量を表11に示した。イノシン及び5'-イノシン酸は、高速液体クロマトグラフィー (HPLC) により、下記の条件にて分析した。

カラム: Cosmosil 5C18-AR (4.6×150mm) [ナカライテスク社製品]

移動相: 5mM リン酸カリウムバッファー (pH 2.8) / メタノール = 95/5

流速: 1.0ml/min

温度: 室温

検出: UV245nm

エシェリヒア・コリ J M109/pENP170ではIPTG無添加では活性が低かったが、エシェリヒア・コリ J M109/pENP180はIPTGを添加しなくても高い活性を示した。また、エシェリヒア・コリ J M109/pENP180はIPTGを添加することでさらに高い活性を発現し、プロモーター領域の改変が有効であることが示された。

【0053】

【表11】

菌 株	IPTG	生成 5'-イノシン酸 (g/dl)
エシェリヒア・コリ J M109/pENP170	無添加	0.73
	1 mM 添加	3.09
エシェリヒア・コリ J M109/pENP180	無添加	2.86
	1 mM 添加	3.37

【0054】実施例22 ヌクレオシドに対する親和性の向上したエンテロバクター・アエロゲネス IF0 12010

由来新規変異型酸性ホスファターゼ遺伝子の構築

実施例21にて構築したエンテロバクター・アエロゲネス IF0 12010由来変異型酸性ホスファターゼ遺伝子に遺伝子工学的手法によって部位特異的変異を導入し、ヌクレオシド、特にグアノシンに対する親和性が向上した変異型酸性ホスファターゼをコードする遺伝子を作製した。アミノ酸残基の置換はエシェリヒア・ブラウタエ酵素の立体構造解析に基づいてヌクレオシドとの親和性向上に寄与すると同定されたアミノ酸残基の置換を組合せて導入した。プラスミドDNAへの変異導入はストラタジーン社製のクイックチェンジ部位特異的突然変異誘発キット (Quick Change site-directed mutagenesis kit) を用いた。DNA合成装置 (アプライドバイオシステム社製モデル394) を用いてMUT180 (配列表の配列番号101) からMUT521 (配列表の配列番号120) までの20種類の変異導入用オリゴヌクレオチドを合成した。最初の鋳型としてpENP170、また変異導入用オリゴヌクレオチドとしてMUT180、MUT181を用いてストラタジーン社のプロトコールに従って変異を導入した。得られたプラスミドDNAを用いて常法によりエシェリヒア・コリ J M109 (宝酒造社製) を形質転換した。これを100 µg/mlのアンピシリンを含むL寒天培地上にプレーティングし、形質転換体を得た。形質転換体よりアルカリ溶菌法によりプラスミドを調製し、塩基配列の決定を行い、目的の塩基が置換されていることを確認した。塩基配列の決定は Taq DyeDeoxy Terminator Cycle Sequencing Kit (アプライドバイオケミカル社製) を用い、サンガーらの方法 (前出の学会誌) に従って行った。このようにして153番目のスレオニン残基 (ACC) がセリン

残基 (TCC) に置換した変異型酸性ホスファターゼをコードする遺伝子を構築し、この変異型遺伝子を含むプラスミドをpENP200と命名した。変異を導入したプラスミドを新しい鋳型として同様の操作を繰り返し、累加的に部位特異的変異を導入した。形質転換体よりアルカリ溶菌法によりプラスミドを調製し、塩基配列の決定を行い、目的の塩基が置換されていることを確認した。作成した変異型酸性ホスファターゼをコードする変異型酵素遺伝子と変異部位を表12に示した。なお変異部位のアミノ酸残基は配列表の配列番号10に示した成熟蛋白質のアミノ酸配列中のアミノ酸残基を示している。

【0055】それぞれの変異型酸性ホスファターゼ遺伝子を含むプラスミドを導入したエシェリヒア・コリ J M109/pENP180、エシェリヒア・コリ J M109/pENP320、エシェリヒア・コリ J M109/pENP340、エシェリヒア・コリ J M109/pENP410、エシェリヒア・コリ J M109/pENP510、及びエシェリヒア・コリ J M109/pENP520をアンピシリン100 µg/ml及びIPTG1mMを含むL培地50mlに接種し、37℃で16時間培養した。菌体を50mlの100mMリン酸バッファー (pH7.0) に懸濁し、4℃で20分間超音波処理を行い菌体を破碎した。それぞれの菌の培養液から遠心分離により菌体を集め、生理食塩水で1回洗浄した。処理液を遠心分離して不溶性画分を除き、無細胞抽出液を調製した。それぞれの無細胞抽出液を用いてリン酸転移反応におけるイノシンとグアノシンに対するKm値を測定した。

【0056】ヌクレオシドへのリン酸転移活性の測定は、イノシン及びグアノシンを基質として次の条件で行った。各種濃度のイノシン又はグアノシン、ピロリン酸ナトリウム100 µmol/ml、酢酸ナトリウム緩衝液 (pH4.0) 100 µmol/ml及び酵素を含む反応液 (1ml) でpH4.0、



30℃で10分反応を行った。2N塩酸200 $\mu$ lを添加して反応を停止した後、遠心分離により沈殿を除き、リン酸転移反応により生成した5'-イノシン酸又は5'-グアニル酸を定量した。イノシン、グアノシン、5'-イノシン酸及び5'-グアニル酸は、高速液体クロマトグラフィー（HPLC）により、実施例21と同じ条件にて分析した。上記の組成の反応条件においてイノシン又はグアノシンの濃度を変化させてリン酸転移活性を測定し、Hanes-Woolfプロット〔ザ バイオケミカル ジャーナル（Biochem. J.）、第26巻、第1406頁（1932）〕により

リン酸転移反応におけるイノシン及びグアノシンの速度定数を求めた。その結果を表13～表16に示した。実施例で作成した変異型酵素のKm値はグアノシンに対するKm値が顕著に低下し、グアノシンに対する親和性が向上していることが明らかになった。またpENP520にコードされる変異型酵素以外の4種類の変異型酵素はイノシンに対するKm値も非常に低下していた。

【0057】

【表12】

配列の名称	配列番号	センス	長さ	配列
MUT170	99	センス	30	5'-CTT ACA GAT GAC <u>TAT</u> <u>AAT</u> GTG ACT AAA AAC
MUT171	100	アンチセンス	30	5'-GTT TTT AGT CAC ATT ATA GTC ATC TGT AAG
MUT180	101	センス	33	5'-TCT ACC GGT TGG GCA <u>TCC</u> GCG CTG GTA CTG GCG
MUT181	102	アンチセンス	33	5'-CGC CAG TAC CAG CGC <u>GGA</u> TGC CCA ACC GGT AGA
MUT300	103	センス	33	5'-TCC GGC CAT ACC TCT <u>TCC</u> GGT TGG GCA TCC GCG
MUT301	104	アンチセンス	33	5'-CGC GGA TGC CCA ACC <u>GGA</u> AGA GGT ATG GCC GGA
MUT310	105	センス	33	5'-GAT GCT GAC CTG GCC <u>GTT</u> GGC GAC GTC GCG AAT
MUT311	106	アンチセンス	33	5'-ATT CGC GAC GTC GCC <u>AAC</u> GGC CAG GTC AGC ATC
MUT320	107	センス	33	5'-CTG ACA AAT ATG ATT <u>CTG</u> GAT GCC GGC GAT CTG
MUT321	108	アンチセンス	33	5'-CAG ATC GCC GGC ATC CAG AAT CAT ATT TGT CAG
MUT330	109	センス	33	5'-GAT GCT GAC CTG GCC <u>ATG</u> GGC GAC GTC GCG AAT
MUT331	110	アンチセンス	33	5'-ATT CGC GAC GTC GCC <u>CAT</u> GGC CAG GTC AGC ATC
MUT340	111	センス	33	5'-CTG ACA AAT ATG ATT <u>CAG</u> GAT GCC GGC GAT CTG
MUT341	112	アンチセンス	33	5'-CAG ATC GCC GGC ATC <u>CTG</u> AAT CAT ATT TGT CAG
MUT400	113	センス	33	5'-TCC GGC CAT ACC TCT <u>GCT</u> GGT TGG GCA TCC GCG
MUT401	114	アンチセンス	33	5'-CGC GGA TGC CCA ACC AGC AGA GGT ATG GCC GGA
MUT500	115	センス	33	5'-TCC GGC CAT ACC TCT <u>GGC</u> GGT TGG GCA TCC GCG
MUT501	116	アンチセンス	33	5'-CGC GGA TGC CCA ACC <u>GCC</u> AGA GGT ATG GCC GGA
MUT510	117	センス	33	5'-GAT GCT GAC CTG GCC <u>GAA</u> GGC GAC GTC GCG AAT
MUT511	118	アンチセンス	33	5'-ATT CGC GAC GTC GCC <u>TTC</u> GGC CAG GTC AGC ATC
MUT520	119	センス	33	5'-GAT GCT GAC CTG GCC <u>AAA</u> GGC GAC GTC GCG AAT
MUT521	120	アンチセンス	33	5'-ATT CGC GAC GTC GCC <u>TTT</u> GGC CAG GTC AGC ATC

【0058】

【表13】

プラスミド名	変異を導入したプラスミド	変異導入に用いたプライマー	変異点及びアミノ酸置換
pENP180			61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151I(ATC)→T(ACC)
pENP200	pENP130	MUT180, MUT181	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151T(ACC)→S(TCC)
pENP300	pENP200	MUT300, MUT301	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151I(ATC)→T(ACC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP310	pENP300	MUT310, MUT311	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→V(GTT) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 151I(ATC)→T(ACC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP320	pENP310	MUT320, MUT321	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC)

【0059】

【表14】

			69S(AGC)→A(GCC) 70A(GCC)→V(GTT) 72G(GGC)→D(GAC) 102E(GAG)→L(CTG) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP330	pENP300	MUT330, MUT331	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→M(ATG) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP340	pENP330	MUT340, MUT341	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→V(GTT) 72G(GGC)→D(GAC) 102E(GAG)→Q(CAG) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→S(TCC) 151T(ACC)→S(TCC)
pENP400	pENP200	MUT400, MUT401	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→A(GCT) 151T(ACC)→S(TCC)
pENP410	pENP400	MUT310, MUT311	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→V(GTT) 72G(GGC)→D(GAC)

【0060】

【表15】

			133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→A(GCT) 151T(ACC)→S(TCC)
pENP500	pENP200	MUT500, MUT501	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→G(GGC) 151T(ACC)→S(TCC)
pENP510	pENP500	MUT510, MUT511	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→E(GAA) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→G(GGC) 151T(ACC)→S(TCC)
pENP520	pENP500	MUT520, MUT521	61L(CTG)→Q(CAG) 63A(GCT)→Q(CAG) 64E(GAA)→A(GCA) 67N(AAC)→D(GAC) 69S(AGC)→A(GCC) 70A(GCC)→K(AAA) 72G(GGC)→D(GAC) 133T(ACC)→K(AAA) 134E(GAG)→D(GAC) 149T(ACC)→G(GGC) 151T(ACC)→S(TCC)

【0061】

【表16】

	イノシンに対する Km 値 (mM)	イノシンを基質とした場合 の相対活性	グアノシンに対する Km 値 (mM)	グアノシンを 基質とした時の 相対活性
pENP180	4.0	1.0	4.0	1.0
pENP320	1.9	1.9	4.6	1.5
pENP340	1.9	1.4	5.1	1.3
pENP410	1.8	1.0	4.9	0.70
pENP510	1.7	0.55	4.0	0.39
pENP520	4.6	0.63	4.4	0.21

【0062】実施例23 グアノシンに対する親和性の向上したエンテロバクター・アエロゲネス IF0 12010 由来新規変異型酸性ホスファターゼ遺伝子導入菌によるグアノシンのリン酸化反応  
それぞれの変異型酸性ホスファターゼ遺伝子を含むプラスミドを導入したエシェリヒア・コリ J M109/pENP180、エシェリヒア・コリ J M109/pENP320、エシェリヒア・コリ J M109/pENP340、エシェリヒア・コリ J M109/pENP410、エシェリヒア・コリ J M109/pENP510、及びエシェリヒア・コリ J M109/pENP520をアンピシリン

100 µg/ml 及び IPTG 1mM を含む L 培地 50ml に接種し、37℃で16時間培養した。ピロリン酸 10g/dl、及び特開平12-189226号公報の実施例1と同様に調製した粉碎グアノシン 6.6g/dl を 100mM 酢酸バッファー (pH4.5) に溶解し、これにそれぞれの菌体を乾燥菌体重量で 100 mg/dl となるように添加し、pH を 4.5 に維持しながら、35℃で12時間反応させた。生成した5'-グアニル酸の量を表17に示した。表17に示すように変異型酵素を導入した菌はいずれも親株であるエシェリヒア・コリ J M109/pENP180 に比べて生産性が向上し、高い収率で5'

ーグアニル酸を生成蓄積した。

【表17】

【0063】

菌 株	生成 5'-グアニル酸 (g/dl)
エシェリヒア・コリ JM109/pENP180	9.90
エシェリヒア・コリ JM109/pENP320	10.4
エシェリヒア・コリ JM109/pENP340	10.2
エシェリヒア・コリ JM109/pENP410	11.1
エシェリヒア・コリ JM109/pENP510	11.0
エシェリヒア・コリ JM109/pENP520	10.5

【0064】

【発明の効果】以上詳細に説明したように、本発明によれば、ヌクレオシドー5'-リン酸生産能が向上した変異型ヌクレオシドー5'-リン酸生産酵素、及びその製造方法が提供される。また、本発明によれば、ヌクレオシドー5'-リン酸の製造方法に有用な、前記の変異型

酵素をコードする遺伝子、該遺伝子を含む組換えDNA

A、該組換えDNAを保有する微生物が提供される。更に、X線結晶構造解析技術により蛋白質の新規立体構造の解明に成功した。

【0065】

【配列表】

<110>: Ajinomoto Co., Inc. (味の素株式会社)  
 <120>: 変異型ヌクレオシドー5'-リン酸生産酵素  
 <130>: 整理番号 1-000804-1  
 <141>: 2000-09-03  
 <150>: JP 11-249545  
 <151>: 1999-09-03  
 <160>:  
 <170>: PatentIn Ver. 2.0

【0066】

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 <213>: Escherichia blattae  
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 <221>: CDS  
 <222>: (331).. (1077)  
 <400>: 1  
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 taactatcca ttattacagg taacagcatt gctcctgagt gtgatgtcat acctgagcgg 120  
 cgcgggggtt ccccgggccg ctttttttta tggggctgcg gtgaggagcg ttatctgctg 180  
 gccctgtttg tgcaacaaac gcttttatgt tgtaattttt gtgacgtata tcagggtttt 240  
 aagcaccctg tggcgctcat actggcaacc tgttgatatt aagcaacact cttcactcac 300  
 ggaattaaca cgcacagtaa aggtatacgc atg aaa aaa cgt gtt ctg gca gtt 354  
 Met Lys Lys Arg Val Leu Ala Val  
 1 5  
 tgt ttt gcc gca ttg ttc tct tct cag gcc ctg gcg ctg gtc gct acc 402  
 Cys Phe Ala Ala Leu Phe Ser Ser Gln Ala Leu Ala Leu Val Ala Thr  
 10 15 20  
 ggc aac gac act acc acg aaa ccg gat ctc tac tac ctc aag aac agt 450  
 Gly Asn Asp Thr Thr Thr Lys Pro Asp Leu Tyr Tyr Leu Lys Asn Ser  
 25 30 35 40

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gaa gcc att aac agc ctg gcg ctg ttg ccg cca cca ccg gcg gtg ggc 498
Glu Ala Ile Asn Ser Leu Ala Leu Leu Pro Pro Pro Pro Ala Val Gly
          45          50          55
tcc att gcg ttt ctc aac gat cag gcc atg tat gaa cag ggg cgc ctg 546
Ser Ile Ala Phe Leu Asn Asp Gln Ala Met Tyr Glu Gln Gly Arg Leu
          60          65          70
ctg cgc aac acc gaa cgc ggt aag ctg gcg gcg gaa gat gca aac ctg 594
Leu Arg Asn Thr Glu Arg Gly Lys Leu Ala Ala Glu Asp Ala Asn Leu
          75          80          85
agc agt ggc ggg gtg gcg aat gct ttc tcc ggc gcg ttt ggt agc ccg 642
Ser Ser Gly Gly Val Ala Asn Ala Phe Ser Gly Ala Phe Gly Ser Pro
          90          95          100
atc acc gaa aaa gac gcc ccg gcg ctg cat aaa tta ctg acc aat atg 690
Ile Thr Glu Lys Asp Ala Pro Ala Leu His Lys Leu Leu Thr Asn Met
105          110          115          120
att gag gac gcc ggg gat ctg gcg acc cgc agc gcg aaa gat cac tat 738
Ile Glu Asp Ala Gly Asp Leu Ala Thr Arg Ser Ala Lys Asp His Tyr
          125          130          135
atg cgc att cgt ccg ttc gcg ttt tat ggg gtc tct acc tgt aat acc 786
Met Arg Ile Arg Pro Phe Ala Phe Tyr Gly Val Ser Thr Cys Asn Thr
          140          145          150
acc gag cag gac aaa ctg tcc aaa aat ggc tct tat ccg tcc ggg cat 834
Thr Glu Gln Asp Lys Leu Ser Lys Asn Gly Ser Tyr Pro Ser Gly His
          155          160          165
acc tct atc ggc tgg gct act gcg ctg gtg ctg gca gag atc aac cct 882
Thr Ser Ile Gly Trp Ala Thr Ala Leu Val Leu Ala Glu Ile Asn Pro
          170          175          180
cag cgc cag aac gag atc ctg aaa cgc ggt tat gag ctg ggc cag agc 930
Gln Arg Gln Asn Glu Ile Leu Lys Arg Gly Tyr Glu Leu Gly Gln Ser
185          190          195          200
cgg gtg att tgc ggc tac cac tgg cag agt gat gtg gat gcc gcg cgg 978
Arg Val Ile Cys Gly Tyr His Trp Gln Ser Asp Val Asp Ala Ala Arg
          205          210          215
gta gtg gga tct gcc gtt gtg gcg acc ctg cat acc aac ccg gcg ttc 1026
Val Val Gly Ser Ala Val Val Ala Thr Leu His Thr Asn Pro Ala Phe
          220          225          230
cag cag cag ttg cag aaa gcg aag gcc gaa ttc gcc cag cat cag aag 1074
Gln Gln Gln Leu Gln Lys Ala Lys Ala Glu Phe Ala Gln His Gln Lys
          235          240          245
aaa taatcctgac taccgccttg ccttcaggg cggtagtggg ttccactggc 1127
Lys
cccgattcgc tattccaca gtaataatga cggtatatga tttgtgcaa cgaaaaggtt 1187
gtgtcacgcc acagcttata agatcatgtg ccgttaac 1225

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【0067】

&lt;:210&gt;; 2

&lt;:211&gt;; 249

&lt;:212&gt;; PRT

&lt;:213&gt;; Escherichia blattae

&lt;:400&gt;; 2

Met Lys Lys Arg Val Leu Ala Val Cys Phe Ala Ala Leu Phe Ser Ser

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Gln Ala Leu Ala Leu Val Ala Thr Gly Asn Asp Thr Thr Thr Lys Pro
      20           25           30
Asp Leu Tyr Tyr Leu Lys Asn Ser Glu Ala Ile Asn Ser Leu Ala Leu
      35           40           45
Leu Pro Pro Pro Pro Ala Val Gly Ser Ile Ala Phe Leu Asn Asp Gln
      50           55           60
Ala Met Tyr Glu Gln Gly Arg Leu Leu Arg Asn Thr Glu Arg Gly Lys
      65           70           75           80
Leu Ala Ala Glu Asp Ala Asn Leu Ser Ser Gly Gly Val Ala Asn Ala
      85           90           95
Phe Ser Gly Ala Phe Gly Ser Pro Ile Thr Glu Lys Asp Ala Pro Ala
      100          105          110
Leu His Lys Leu Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala
      115          120          125
Thr Arg Ser Ala Lys Asp His Tyr Met Arg Ile Arg Pro Phe Ala Phe
      130          135          140
Tyr Gly Val Ser Thr Cys Asn Thr Thr Glu Gln Asp Lys Leu Ser Lys
      145          150          155          160
Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Ile Gly Trp Ala Thr Ala
      165          170          175
Leu Val Leu Ala Glu Ile Asn Pro Gln Arg Gln Asn Glu Ile Leu Lys
      180          185          190
Arg Gly Tyr Glu Leu Gly Gln Ser Arg Val Ile Cys Gly Tyr His Trp
      195          200          205
Gln Ser Asp Val Asp Ala Ala Arg Val Val Gly Ser Ala Val Val Ala
      210          215          220
Thr Leu His Thr Asn Pro Ala Phe Gln Gln Gln Leu Gln Lys Ala Lys
      225          230          235          240
Ala Glu Phe Ala Gln His Gln Lys Lys
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【0068】

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cttattttatc cgttcgtaa caaaagccat gctgtttctg tcaaattatc tgaaaatcat 180
catcaaaaat acttacctgt cttccgtctg ttccgtcaca cttttttgaa agagttaaca 240
tcaatttgca tctctccgcc ctacactggc agacagggtt ctgagtaata ctgttgtatc 300
tgataaggag atgtc atg aag aag aat att atc gcc ggt tgt ctg ttc tca 351
      Met Lys Lys Asn Ile Ile Ala Gly Cys Leu Phe Ser
      1           5           10
ctg ttt tcc ctt tcc gcg ctg gcc gcg atc ccg gcg ggc aac gat gcc 399
Leu Phe Ser Leu Ser Ala Leu Ala Ala Ile Pro Ala Gly Asn Asp Ala

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Thr Thr Lys Pro Asp Leu Tyr Tyr Leu Lys Asn Glu Gln Ala Ile Asp
      30              35              40
agc ctg aaa ctg tta ccg cca ccg ccg gaa gtc ggc agt att cag ttt 495
Ser Leu Lys Leu Leu Pro Pro Pro Pro Glu Val Gly Ser Ile Gln Phe
      45              50              55              60
tta aat gat cag gca atg tat gag aaa ggc cgt atg ctg cgc aat acc 543
Leu Asn Asp Gln Ala Met Tyr Glu Lys Gly Arg Met Leu Arg Asn Thr
      65              70              75
gag cgc gga aaa cag gca cag gca gat gct gac ctg gcc gca ggg ggt 591
Glu Arg Gly Lys Gln Ala Gln Ala Asp Ala Asp Leu Ala Ala Gly Gly
      80              85              90
gtg gca acc gca ttt tca ggg gca ttc ggc tat ccg ata acc gaa aaa 639
Val Ala Thr Ala Phe Ser Gly Ala Phe Gly Tyr Pro Ile Thr Glu Lys
      95              100              105
gac tct ccg gag ctg tat aaa ctg ctg acc aat atg att gag gat gcc 687
Asp Ser Pro Glu Leu Tyr Lys Leu Leu Thr Asn Met Ile Glu Asp Ala
      110              115              120
ggg gat ctt gcc acc cgc tcc gcc aaa gaa cat tac atg cgc atc cgg 735
Gly Asp Leu Ala Thr Arg Ser Ala Lys Glu His Tyr Met Arg Ile Arg
      125              130              135              140
ccg ttt gcg ttt tac ggc aca gaa acc tgt aat acc aaa gat cag aaa 783
Pro Phe Ala Phe Tyr Gly Thr Glu Thr Cys Asn Thr Lys Asp Gln Lys
      145              150              155
aaa ctc tcc acc aac gga tct tac ccg tca ggt cat acg tct atc ggc 831
Lys Leu Ser Thr Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Ile Gly
      160              165              170
tgg gca acc gca ctg gtg ctg gcg gaa gtg aac ccg gca aat cag gat 879
Trp Ala Thr Ala Leu Val Leu Ala Glu Val Asn Pro Ala Asn Gln Asp
      175              180              185
gcg att ctg gaa cgg ggt tat cag ctc gga cag agc cgg gtg att tgc 927
Ala Ile Leu Glu Arg Gly Tyr Gln Leu Gly Gln Ser Arg Val Ile Cys
      190              195              200
ggc tat cac tgg cag agt gat gtg gat gcc gcg cgg att gtc ggt tca 975
Gly Tyr His Trp Gln Ser Asp Val Asp Ala Ala Arg Ile Val Gly Ser
      205              210              215              220
gcc gct gtc gcg aca tta cat tcc gat ccg gca ttt cag gcg cag tta 1023
Ala Ala Val Ala Thr Leu His Ser Asp Pro Ala Phe Gln Ala Gln Leu
      225              230              235
gcg aaa gcc aaa cag gaa ttt gca caa aaa tca cag aaa taaaagcagt 1072
Ala Lys Ala Lys Gln Glu Phe Ala Gln Lys Ser Gln Lys
      240              245
gatatctggt cagggcagtg caatatctgc cctgaaatcc ctgtttattc ccacatccag 1132
cggttcttccc gatccagccc tttgttttc atgcagctgt agaaatagcg gttgcggctg 1192
tcttcattca catccatcac ataactttcc gttaccggtg tctgctcttt gtaggttttg 1252
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tgagcaactt catttttcac cggataaagc tt 1344

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 Ser Ala Leu Ala Ala Ile Pro Ala Gly Asn Asp Ala Thr Thr Lys Pro  
                     20                    25                    30  
 Asp Leu Tyr Tyr Leu Lys Asn Glu Gln Ala Ile Asp Ser Leu Lys Leu  
             35                    40                    45  
 Leu Pro Pro Pro Pro Glu Val Gly Ser Ile Gln Phe Leu Asn Asp Gln  
             50                    55                    60  
 Ala Met Tyr Glu Lys Gly Arg Met Leu Arg Asn Thr Glu Arg Gly Lys  
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 Gln Ala Gln Ala Asp Ala Asp Leu Ala Ala Gly Gly Val Ala Thr Ala  
                     85                    90                    95  
 Phe Ser Gly Ala Phe Gly Tyr Pro Ile Thr Glu Lys Asp Ser Pro Glu  
             100                    105                    110  
 Leu Tyr Lys Leu Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala  
             115                    120                    125  
 Thr Arg Ser Ala Lys Glu His Tyr Met Arg Ile Arg Pro Phe Ala Phe  
             130                    135                    140  
 Tyr Gly Thr Glu Thr Cys Asn Thr Lys Asp Gln Lys Lys Leu Ser Thr  
     145                    150                    155                    160  
 Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Ile Gly Trp Ala Thr Ala  
                     165                    170                    175  
 Leu Val Leu Ala Glu Val Asn Pro Ala Asn Gln Asp Ala Ile Leu Glu  
             180                    185                    190  
 Arg Gly Tyr Gln Leu Gly Gln Ser Arg Val Ile Cys Gly Tyr His Trp  
             195                    200                    205  
 Gln Ser Asp Val Asp Ala Ala Arg Ile Val Gly Ser Ala Ala Val Ala  
             210                    215                    220  
 Thr Leu His Ser Asp Pro Ala Phe Gln Ala Gln Leu Ala Lys Ala Lys  
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 Gln Glu Phe Ala Gln Lys Ser Gln Lys  
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【0070】

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 <213>; *Salmonella typhimurium*  
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 tgaataacca ttgcaataaa tcattatagg attacatctg ttattatttg cctgatccgg 120  
 agtgagtctt t atg aaa agt cgt tat tta gta ttt ttt cta cca ctg atc 170  
     Met Lys Ser Arg Tyr Leu Val Phe Phe Leu Pro Leu Ile  
             1                    5                    10

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gta gct aaa tat aca tca gca gaa aca gtg caa ccc ttt cat tct cct 218
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      15              20              25
gaa gaa tca gtg aac agt cag ttc tac tta cca cca ccg cca ggt aat 266
Glu Glu Ser Val Asn Ser Gln Phe Tyr Leu Pro Pro Pro Pro Gly Asn
      30              35              40              45
gat gat ccg gct tac cgc tat gat aag gag gct tat ttt aag ggc tat 314
Asp Asp Pro Ala Tyr Arg Tyr Asp Lys Glu Ala Tyr Phe Lys Gly Tyr
              50              55              60
gcg ata aag ggt tcc ccg cga tgg aaa caa gct gct gag gat gca gat 362
Ala Ile Lys Gly Ser Pro Arg Trp Lys Gln Ala Ala Glu Asp Ala Asp
              65              70              75
gta agc gtg gaa aat ata gcc aga ata ttc tcg cca gta gtg ggt gct 410
Val Ser Val Glu Asn Ile Ala Arg Ile Phe Ser Pro Val Val Gly Ala
              80              85              90
aaa att aac ccc aaa gat acg cca gaa acc tgg aat atg tta aag aat 458
Lys Ile Asn Pro Lys Asp Thr Pro Glu Thr Trp Asn Met Leu Lys Asn
              95              100              105
ctt ctg aca atg ggc ggc tac tac gct act gct tcg gca aaa aaa tat 506
Leu Leu Thr Met Gly Gly Tyr Tyr Ala Thr Ala Ser Ala Lys Lys Tyr
      110              115              120              125
tat atg cgt acc cgc ccc ttt gtc tta ttt aat cat tcc acc tgc cgt 554
Tyr Met Arg Thr Arg Pro Phe Val Leu Phe Asn His Ser Thr Cys Arg
              130              135              140
cct gaa gat gag aat act ttg cga aaa aat ggc tct tac cct tcc ggg 602
Pro Glu Asp Glu Asn Thr Leu Arg Lys Asn Gly Ser Tyr Pro Ser Gly
              145              150              155
cat act gct tat ggt aca ctt ctg gca tta gta tta tcc gag gcc aga 650
His Thr Ala Tyr Gly Thr Leu Leu Ala Leu Val Leu Ser Glu Ala Arg
              160              165              170
ccg gaa cgc gcg cag gag ctc gcc aga cgc gga tgg gag ttc ggg caa 698
Pro Glu Arg Ala Gln Glu Leu Ala Arg Arg Gly Trp Glu Phe Gly Gln
              175              180              185
agc aga gtg ata tgc ggt gct cac tgg caa agc gat gtt gat gct ggc 746
Ser Arg Val Ile Cys Gly Ala His Trp Gln Ser Asp Val Asp Ala Gly
      190              195              200              205
cgt tat gtg gga gca gta gag ttt gca aga ctg caa aca atc ccg gct 794
Arg Tyr Val Gly Ala Val Glu Phe Ala Arg Leu Gln Thr Ile Pro Ala
              210              215              220
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Phe Gln Lys Ser Leu Ala Lys Ser Val Arg Ser
              225              230
ttgagtaaag aagatcaccc caaacttaat tactgaaggt gaaagtcttc ccgcaaactg 907
gccacagcaa atgaaaggaa gtgcaactgc gtaggggcgg ccgggcgtgg agaatgcctt 967
tggtttcccc gattcgcatg aatt 991

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【0071】

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<:211>; 232
<:212>; PRT
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 Val Asn Ser Gln Phe Tyr Leu Pro Pro Pro Pro Gly Asn Asp Asp Pro  
 35 40 45  
 Ala Tyr Arg Tyr Asp Lys Glu Ala Tyr Phe Lys Gly Tyr Ala Ile Lys  
 50 55 60  
 Gly Ser Pro Arg Trp Lys Gln Ala Ala Glu Asp Ala Asp Val Ser Val  
 65 70 75 80  
 Glu Asn Ile Ala Arg Ile Phe Ser Pro Val Val Gly Ala Lys Ile Asn  
 85 90 95  
 Pro Lys Asp Thr Pro Glu Thr Trp Asn Met Leu Lys Asn Leu Leu Thr  
 100 105 110  
 Met Gly Gly Tyr Tyr Ala Thr Ala Ser Ala Lys Lys Tyr Tyr Met Arg  
 115 120 125  
 Thr Arg Pro Phe Val Leu Phe Asn His Ser Thr Cys Arg Pro Glu Asp  
 130 135 140  
 Glu Asn Thr Leu Arg Lys Asn Gly Ser Tyr Pro Ser Gly His Thr Ala  
 145 150 155 160  
 Tyr Gly Thr Leu Leu Ala Leu Val Leu Ser Glu Ala Arg Pro Glu Arg  
 165 170 175  
 Ala Gln Glu Leu Ala Arg Arg Gly Trp Glu Phe Gly Gln Ser Arg Val  
 180 185 190  
 Ile Cys Gly Ala His Trp Gln Ser Asp Val Asp Ala Gly Arg Tyr Val  
 195 200 205  
 Gly Ala Val Glu Phe Ala Arg Leu Gln Thr Ile Pro Ala Phe Gln Lys  
 210 215 220  
 Ser Leu Ala Lys Ser Val Arg Ser  
 225 230

[0072]

&lt;;210&gt;; 7

&lt;;211&gt;; 1335

&lt;;212&gt;; DNA

<;213>; *Zymomonas mobilis*

&lt;;220&gt;;

&lt;;221&gt;; CDS

&lt;;222&gt;; (317)..(1108)

&lt;;400&gt;; 7

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 acgccggaag gcttcatggt cgtcaaagtc gaaaagggtta aagtcattcc gcattacgaa 120  
 agctatggct tccacacgat agacccgcgc aacacataat tgtcttatta tagccacatg 180  
 atatttttat attacaattt taaactaaaa ttaagaatta aattcttgaa ataaaggttt 240  
 ttttattaaa aggataggaa atgtcgtgaa atcggcattt tctatccata ttatataaca 300  
 agggaagact gacgac atg ata aaa gtc ccg cgg ttc atc tgt atg atc gcg 352  
 Met Ile Lys Val Pro Arg Phe Ile Cys Met Ile Ala  
 1 5 10  
 ctt aca tcc ggc gtt ctg gca agc ggc ctt tct caa agc gtt tca gct 400  
 Leu Thr Ser Gly Val Leu Ala Ser Gly Leu Ser Gln Ser Val Ser Ala

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      15          20          25
cat aca gaa aaa agt gaa ccc tcc tcg act tat cat ttc cac agc gat 448
His Thr Glu Lys Ser Glu Pro Ser Ser Thr Tyr His Phe His Ser Asp
      30          35          40
ccc ctt ctt tac ctt gcg ccc cca ccc act tcc ggc agt cca tta cag 496
Pro Leu Leu Tyr Leu Ala Pro Pro Pro Thr Ser Gly Ser Pro Leu Gln
      45          50          55          60
gcg cat gat gat caa acc ttt aac agc acc aga caa tta aaa ggt agc 544
Ala His Asp Asp Gln Thr Phe Asn Ser Thr Arg Gln Leu Lys Gly Ser
      65          70          75
acg cgc tgg gca ttg gca act caa gat gcc gat ctt cat ctc gct tca 592
Thr Arg Trp Ala Leu Ala Thr Gln Asp Ala Asp Leu His Leu Ala Ser
      80          85          90
gtt ctc aaa gac tat gcc tgc gcc gca gga atg aat ctc gat att gcg 640
Val Leu Lys Asp Tyr Ala Cys Ala Ala Gly Met Asn Leu Asp Ile Ala
      95          100          105
caa tta ccg cat ctt gcc aat ttg att aaa cgc gca ctt cgc acc gaa 688
Gln Leu Pro His Leu Ala Asn Leu Ile Lys Arg Ala Leu Arg Thr Glu
      110          115          120
tat gac gat att ggc aga gcc aaa aat aac tgg aat cgc aaa cga cct 736
Tyr Asp Asp Ile Gly Arg Ala Lys Asn Asn Trp Asn Arg Lys Arg Pro
      125          130          135          140
ttt gtg gat acc gat caa ccc atc tgc acg gaa aaa gat cgc gaa ggt 784
Phe Val Asp Thr Asp Gln Pro Ile Cys Thr Glu Lys Asp Arg Glu Gly
      145          150          155
ctg gga aaa caa ggc tcc tat cct tca ggt cat acg act atc ggt tgg 832
Leu Gly Lys Gln Gly Ser Tyr Pro Ser Gly His Thr Thr Ile Gly Trp
      160          165          170
agc gtt gcg ctc att ctg gct gaa ttg atc ccc gat cat gcg gcg aat 880
Ser Val Ala Leu Ile Leu Ala Glu Leu Ile Pro Asp His Ala Ala Asn
      175          180          185
att ttg cag cgt ggc caa att ttt gga acc agc cgg att gtc tgc ggc 928
Ile Leu Gln Arg Gly Gln Ile Phe Gly Thr Ser Arg Ile Val Cys Gly
      190          195          200
gcc cat tgg ttc agc gat gtg cag gca ggc tat atc atg gca tcg ggc 976
Ala His Trp Phe Ser Asp Val Gln Ala Gly Tyr Ile Met Ala Ser Gly
      205          210          215          220
gaa att gca gct tta cat ggg gat gcc gat ttc cgc cga gat atg gaa 1024
Glu Ile Ala Ala Leu His Gly Asp Ala Asp Phe Arg Arg Asp Met Glu
      225          230          235
tta gct cgg aaa gaa tta gaa aag gca cgc aca tca gcg cac acg cca 1072
Leu Ala Arg Lys Glu Leu Glu Lys Ala Arg Thr Ser Ala His Thr Pro
      240          245          250
gac gat ctt cta tgc aag att gaa caa agc gct cgc taaattcaat 1118
Asp Asp Leu Leu Cys Lys Ile Glu Gln Ser Ala Arg
      255          260
caagtattat ttcaacaagg ggaaagattg cttgctgtaa tttttggata tcaaacaggc 1178
gaaaaaatga aagagcgac gctctttcaa aggcaattcg atttagtccg gtggcattct 1238
cacgccacaa accaaatcat aaataaccgc ctcttttccg ccagataact gcaaaattat 1298
agaataccga cagctggaat atcgtcactt ttcctag 1335

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## 【0073】

<:210>; 8  
 <:211>; 264  
 <:212>; PRT  
 <:213>; *Zymomonas mobilis*  
 <:400>; 8  
 Met Ile Lys Val Pro Arg Phe Ile Cys Met Ile Ala Leu Thr Ser Gly  
 1 5 10 15  
 Val Leu Ala Ser Gly Leu Ser Gln Ser Val Ser Ala His Thr Glu Lys  
 20 25 30  
 Ser Glu Pro Ser Ser Thr Tyr His Phe His Ser Asp Pro Leu Leu Tyr  
 35 40 45  
 Leu Ala Pro Pro Pro Thr Ser Gly Ser Pro Leu Gln Ala His Asp Asp  
 50 55 60  
 Gln Thr Phe Asn Ser Thr Arg Gln Leu Lys Gly Ser Thr Arg Trp Ala  
 65 70 75 80  
 Leu Ala Thr Gln Asp Ala Asp Leu His Leu Ala Ser Val Leu Lys Asp  
 85 90 95  
 Tyr Ala Cys Ala Ala Gly Met Asn Leu Asp Ile Ala Gln Leu Pro His  
 100 105 110  
 Leu Ala Asn Leu Ile Lys Arg Ala Leu Arg Thr Glu Tyr Asp Asp Ile  
 115 120 125  
 Gly Arg Ala Lys Asn Asn Trp Asn Arg Lys Arg Pro Phe Val Asp Thr  
 130 135 140  
 Asp Gln Pro Ile Cys Thr Glu Lys Asp Arg Glu Gly Leu Gly Lys Gln  
 145 150 155 160  
 Gly Ser Tyr Pro Ser Gly His Thr Thr Ile Gly Trp Ser Val Ala Leu  
 165 170 175  
 Ile Leu Ala Glu Leu Ile Pro Asp His Ala Ala Asn Ile Leu Gln Arg  
 180 185 190  
 Gly Gln Ile Phe Gly Thr Ser Arg Ile Val Cys Gly Ala His Trp Phe  
 195 200 205  
 Ser Asp Val Gln Ala Gly Tyr Ile Met Ala Ser Gly Glu Ile Ala Ala  
 210 215 220  
 Leu His Gly Asp Ala Asp Phe Arg Arg Asp Met Glu Leu Ala Arg Lys  
 225 230 235 240  
 Glu Leu Glu Lys Ala Arg Thr Ser Ala His Thr Pro Asp Asp Leu Leu  
 245 250 255  
 Cys Lys Ile Glu Gln Ser Ala Arg  
 260

## 【0074】

<:210>; 9  
 <:211>; 1650  
 <:212>; DNA  
 <:213>; *Enterobacter aerogenes*  
 <:220>;  
 <:221>; CDS  
 <:222>; (344)..(1087)  
 <:220>;  
 <:221>; mat#peptide

&lt;;222&gt;; (404).. (1087)

&lt;;220&gt;;

&lt;;221&gt;; sig#peptide

&lt;;222&gt;; (344).. (403)

&lt;;400&gt;; 9

gtcgacaaac ttcgcctgct cgctatgcag aatggtttcc agcacttttag gggaaatttt 60  
 acaaccgcaa ccggctccgt ggctgtattg cgtaaacga atagcttgct cgctcatgga 120  
 catctcctgt cattgcaatc ccgctatggg agcgcccaaa cggcaagggtg ataagtgcga 180  
 cagtccgaaa tcgcgagtgg ttgctcatta agcagacaaa tatgcgtttt tgcgataccg 240  
 aacaattttt tcaatgtgat tttaactttt acttacagat gacaaaaatg tgactaaaaa 300  
 caaaaccatt gttctggaca tataacaccg taaggaaatg tag atg aaa aag cgc 355

Met Lys Lys Arg

-20

gtt ctc gcc ctc tgc ctc gcc agc ctg ttt tcc gtt aac gct ttc gcg 403  
 Val Leu Ala Leu Cys Leu Ala Ser Leu Phe Ser Val Asn Ala Phe Ala  
 -15 -10 -5 -1

ctg gtc cct gcc ggc aat gat gca acc acc aaa ccg gat ctc tat tat 451  
 Leu Val Pro Ala Gly Asn Asp Ala Thr Thr Lys Pro Asp Leu Tyr Tyr  
 1 5 10 15

ctg aaa aat gca cag gcc atc gat agt ctg gcg ctg ttg ccg ccg ccg 499  
 Leu Lys Asn Ala Gln Ala Ile Asp Ser Leu Ala Leu Leu Pro Pro Pro  
 20 25 30

ccg gaa gtt ggc agc atc gca ttt tta aac gat cag gcg atg tat gag 547  
 Pro Glu Val Gly Ser Ile Ala Phe Leu Asn Asp Gln Ala Met Tyr Glu  
 35 40 45

aaa gga cgg ctg ttg cgc aat acc gaa cgt ggc aag cag gcg cag gca 595  
 Lys Gly Arg Leu Leu Arg Asn Thr Glu Arg Gly Lys Gln Ala Gln Ala  
 50 55 60

gat gct gac ctg gcc gcc ggc gac gtc gcg aat gcc ttc tcc agc gct 643  
 Asp Ala Asp Leu Ala Ala Gly Asp Val Ala Asn Ala Phe Ser Ser Ala  
 65 70 75 80

ttt ggt tcg ccc atc acc gaa aaa gac gcg ccg cag tta cat aag ctg 691  
 Phe Gly Ser Pro Ile Thr Glu Lys Asp Ala Pro Gln Leu His Lys Leu  
 85 90 95

ctg aca aat atg att gag gat gcc ggc gat ctg gcc acc cgc agc gcg 739  
 Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala Thr Arg Ser Ala  
 100 105 110

aaa gag aaa tat atg cgc att cgc ccg ttt gcg ttc tac ggc gtt tca 787  
 Lys Glu Lys Tyr Met Arg Ile Arg Pro Phe Ala Phe Tyr Gly Val Ser  
 115 120 125

acc tgt aac act aaa gac cag gac aag ctg tcg aaa aac gga tct tac 835  
 Thr Cys Asn Thr Lys Asp Gln Asp Lys Leu Ser Lys Asn Gly Ser Tyr  
 130 135 140

cct tcc ggc cat acc tct acc ggt tgg gca acc gcg ctg gta ctg gcg 883  
 Pro Ser Gly His Thr Ser Thr Gly Trp Ala Thr Ala Leu Val Leu Ala  
 145 150 155 160

gag atc aat ccg cag cgg caa aac gaa att ctc aaa cgc ggc tat gaa 931  
 Glu Ile Asn Pro Gln Arg Gln Asn Glu Ile Leu Lys Arg Gly Tyr Glu  
 165 170 175

ttg ggc gaa agc cgg gtt atc tgc ggc tat cat tgg cag agc gat gtc 979

```

Leu Gly Glu Ser Arg Val Ile Cys Gly Tyr His Trp Gln Ser Asp Val
      180              185              190
gat gcg gcg cgg ata gtc ggc tgc gcg gtg gtg gcg acc ctg cat acc 1027
Asp Ala Ala Arg Ile Val Gly Ser Ala Val Val Ala Thr Leu His Thr
      195              200              205
aac ccg gcc ttc caa cag cag ttg cag aaa gca aag gat gaa ttc gcc 1075
Asn Pro Ala Phe Gln Gln Gln Leu Gln Lys Ala Lys Asp Glu Phe Ala
      210              215              220
aaa acg cag aag taacgtcatc gccgttgaac tcccgaggc ggcgcttaac 1127
Lys Thr Gln Lys
225
gcgccttctc cgggctaact aatcgacag cgctgtagcc ccggaagcg ccagcgccac 1187
cggggatttt gagatagcca gcaccagtag ttccagccag cgtgatgaat acattaacgg 1247
caggccgcat gagtcgtaga tactgttacc ggtttgcaac tttttaagg tttttcccg 1307
gaggcgccgc gctgcgcctt ctccgggcta ctaaactgca cagcgctgta gccccggtaa 1367
gcggcagcgc caccgggggt aacaagcgca gattcagaag cgcgtgacga acggcgccgt 1427
atccgggccc gtaaacatgg ttgatgcttt taactgcggc gtgccaaggt agaggaaacc 1487
gacaattttg tcctgttcgc gccagccaaa gccttcgagg acaaccggac tctcggttaa 1547
cgcaccgata cgccagatac cgttatagcc ctgcgccact gcggccattt gcatcgccat 1607
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【0075】

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<;210>; 10
<;211>; 248
<;212>; PRT
<;213>; Enterobacter aerogenes
<;400>; 10
Met Lys Lys Arg Val Leu Ala Leu Cys Leu Ala Ser Leu Phe Ser Val
-20              -15              -10              -5
Asn Ala Phe Ala Leu Val Pro Ala Gly Asn Asp Ala Thr Thr Lys Pro
      -1   1              5              10
Asp Leu Tyr Tyr Leu Lys Asn Ala Gln Ala Ile Asp Ser Leu Ala Leu
      15              20              25
Leu Pro Pro Pro Pro Glu Val Gly Ser Ile Ala Phe Leu Asn Asp Gln
      30              35              40
Ala Met Tyr Glu Lys Gly Arg Leu Leu Arg Asn Thr Glu Arg Gly Lys
      45              50              55              60
Gln Ala Gln Ala Asp Ala Asp Leu Ala Ala Gly Asp Val Ala Asn Ala
      65              70              75
Phe Ser Ser Ala Phe Gly Ser Pro Ile Thr Glu Lys Asp Ala Pro Gln
      80              85              90
Leu His Lys Leu Leu Thr Asn Met Ile Glu Asp Ala Gly Asp Leu Ala
      95              100             105
Thr Arg Ser Ala Lys Glu Lys Tyr Met Arg Ile Arg Pro Phe Ala Phe
      110             115             120
Tyr Gly Val Ser Thr Cys Asn Thr Lys Asp Gln Asp Lys Leu Ser Lys
      125             130             135             140
Asn Gly Ser Tyr Pro Ser Gly His Thr Ser Thr Gly Trp Ala Thr Ala
      145             150             155
Leu Val Leu Ala Glu Ile Asn Pro Gln Arg Gln Asn Glu Ile Leu Lys
      160             165             170

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Arg Gly Tyr Glu Leu Gly Glu Ser Arg Val Ile Cys Gly Tyr His Trp  
 175 180 185  
 Gln Ser Asp Val Asp Ala Ala Arg Ile Val Gly Ser Ala Val Val Ala  
 190 195 200  
 Thr Leu His Thr Asn Pro Ala Phe Gln Gln Gln Leu Gln Lys Ala Lys  
 205 210 215 220  
 Asp Glu Phe Ala Lys Thr Gln Lys  
 225

## 【0076】

<;210>; 11  
 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
 <;220>;  
 <;223>; Description of Artificial Sequence:primer  
 <;400>; 11  
 caaacctgag ctttgcgat gtggc 25

## 【0077】

<;210>; 12  
 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
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 <;223>; Description of Artificial Sequence:primer  
 <;400>; 12  
 gtttggaactc gaaaccgcta caccg 25

## 【0078】

<;210>; 13  
 <;211>; 7  
 <;212>; PRT  
 <;213>; Artificial Sequence  
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 <;223>; Description of Artificial Sequence: partial amino  
 acid sequence around mutation  
 <;400>; 13  
 Asn Leu Ser Phe Gly Asp Val  
 1 5

## 【0079】

<;210>; 14  
 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
 <;220>;  
 <;223>; Description of Artificial Sequence:primer  
 <;400>; 14  
 caaacctgag ctacggcgat gtggc 25

## 【0080】

<;210>; 15  
 <;211>; 25



【0081】	<212>; DNA <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence:primer <400>; 15 gtttgactc gatgccgcta caccg	25
【0082】	<210>; 16 <211>; 7 <212>; PRT <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence: partial amino acid sequence around mutation <400>; 16 Asn Leu Ser Tyr Gly Asp Val 1                  5	
【0083】	<210>; 17 <211>; 25 <212>; DNA <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence:primer <400>; 17 caaacctgag ctggggcgat gtggc	25
【0084】	<210>; 18 <211>; 25 <212>; DNA <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence:primer <400>; 18 gtttgactc gaccccgcta caccg	25
【0085】	<210>; 19 <211>; 7 <212>; PRT <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence: partial amino acid sequence around mutation <400>; 19 Asn Leu Ser Trp Gly Asp Val 1                  5	
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【0087】	<210>; 21 <211>; 25 <212>; DNA <213>; Artificial Sequence  <220>; <223>; Description of Artificial Sequence:primer <400>; 21 gtttgactc gctgccgcta caccg	25
【0088】	<210>; 22 <211>; 7 <212>; PRT <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence: partial amino acid sequence around mutation <400>; 22 Asn Leu Ser Asp Gly Asp Val 1                  5	
【0089】	<210>; 23 <211>; 25 <212>; DNA <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence:primer  <400>; 23 caaacctgag cgttggcgat gtggc	25
【0090】	<210>; 24 <211>; 25 <212>; DNA <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence:primer <400>; 24 gtttgactc gcaaccgcta caccg	
	<210>; 25 <211>; 7 <212>; PRT <213>; Artificial Sequence	

<220>  
 <223> Description of Artificial Sequence: partial amino  
 acid sequence around mutation  
 <400> 25  
 Asn Leu Ser Val Gly Asp Val  
 1 5

**【0091】**  
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 <211> 25  
 <212> DNA  
 <213> Artificial Sequence  
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 <400> 26  
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**【0092】**  
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 <211> 25  
 <212> DNA  
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 <220>  
 <223> Description of Artificial Sequence:primer  
 <400> 27  
 gtttgactc gcttcgcta caccg 25

**【0093】**  
 <210> 28  
 <211> 7  
 <212> PRT  
 <213> Artificial Sequence  
 <220>  
 <223> Description of Artificial Sequence: partial amino  
 acid sequence around mutation  
 <400> 28  
 Asn Leu Ser Glu Gly Asp Val  
 1 5

**【0094】**  
 <210> 29  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence  
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 <223> Description of Artificial Sequence:primer  
 <400> 29  
 caaacctgag catggcgat gtggc 25

**【0095】**  
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 <211> 25  
 <212> DNA  
 <213> Artificial Sequence

	<;220>;	
	<;223>; Description of Artificial Sequence:primer	
	<;400>; 30	
【0096】	gtttggactc gtaccgcta caccg	25
	<;210>; 31	
	<;211>; 7	
	<;212>; PRT	
	<;213>; Artificial Sequence	
	<;220>;	
	<;223>; Description of Artificial Sequence: partial amino acid sequence around mutation	
	<;400>; 31	
	Asn Leu Ser Met Gly Asp Val	
	1 5	
【0097】	<;210>; 32	
	<;211>; 25	
	<;212>; DNA	
	<;213>; Artificial Sequence	
	<;220>;	
	<;223>; Description of Artificial Sequence:primer	
	<;400>; 32	
【0098】	caaacctgag caccggcgat gtggc	25
	<;210>; 33	
	<;211>; 25	
	<;212>; DNA	
	<;213>; Artificial Sequence	
	<;220>;	
	<;223>; Description of Artificial Sequence:primer	
	<;400>; 33	
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	<;210>; 34	
	<;211>; 7	
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	<;213>; Artificial Sequence	
	<;220>;	
	<;223>; Description of Artificial Sequence: partial amino acid sequence around mutation	
	<;400>; 34	
	Asn Leu Ser Thr Gly Asp Val	
	1 5	
【0100】	<;210>; 35	
	<;211>; 25	
	<;212>; DNA	
	<;213>; Artificial Sequence	

<;220>;  
 <;223>; Description of Artificial Sequence:primer  
 <;400>; 35  
 caaacctgag cctgggcgat gtggc 25  
**【0101】**  
 <;210>; 36  
 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
 <;220>;  
 <;223>; Description of Artificial Sequence:primer  
 <;400>; 36  
 gtttgactc ggaccgcta caccg 25  
**【0102】**  
 <;210>; 37  
 <;211>; 7  
 <;212>; PRT  
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 <;220>;  
 <;223>; Description of Artificial Sequence: partial amino  
 acid sequence around mutation  
 <;400>; 37  
 Asn Leu Ser Leu Gly Asp Val  
 1 5  
**【0103】**  
 <;210>; 38  
 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
 <;220>;  
 <;223>; Description of Artificial Sequence:primer  
 <;400>; 38  
 caaacctgag ccgtggcgat gtggc 25  
**【0104】**  
 <;210>; 39  
 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
 <;220>;  
 <;223>; Description of Artificial Sequence:primer  
 <;400>; 39  
 gtttgactc ggcaccgcta caccg 25  
**【0105】**  
 <;210>; 40  
 <;211>; 7  
 <;212>; PRT  
 <;213>; Artificial Sequence  
 <;220>;  
 <;223>; Description of Artificial Sequence: partial amino  
 acid sequence around mutation

	<;400>; 40 Asn Leu Ser Arg Gly Asp Val 1                    5	
【0106】	<;210>; 41 <;211>; 25 <;212>; DNA <;213>; Artificial Sequence <;220>; <;223>; Description of Artificial Sequence:primer <;400>; 41 caaacctgag ccaggcgcat gtggc	25
【0107】	<;210>; 42 <;211>; 25 <;212>; DNA <;213>; Artificial Sequence <;220>; <;223>; Description of Artificial Sequence:primer <;400>; 42 gtttgactc ggtcccgcta caccg	25
【0108】	<;210>; 43 <;211>; 7 <;212>; PRT <;213>; Artificial Sequence <;220>; <;223>; Description of Artificial Sequence: partial amino acid sequence around mutation <;400>; 43 Asn Leu Ser Gln Gly Asp Val 1                    5	
【0109】	<;210>; 44 <;211>; 25 <;212>; DNA <;213>; Artificial Sequence <;220>; <;223>; Description of Artificial Sequence:primer <;400>; 44 caaacctgag caaaggcgat gtggc	25
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## 【0111】

<210> 46  
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 <212> PRT  
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 <220>  
 <223> Description of Artificial Sequence: partial amino  
 acid sequence around mutation

<400> 46  
 Asn Leu Ser Lys Gly Asp Val  
 1 5

## 【0112】

<210> 47  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence  
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 <223> Description of Artificial Sequence: primer  
 <400> 47

caaacctgag cccgggcgat gtggc

25

## 【0113】

<210> 48  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence  
 <220>  
 <223> Description of Artificial Sequence: primer  
 <400> 48

gtttggactc gggcccgcta caccg

25

## 【0114】

<210> 49  
 <211> 7  
 <212> PRT  
 <213> Artificial Sequence  
 <220>  
 <223> Description of Artificial Sequence: partial amino  
 acid sequence around mutation

<400> 49  
 Asn Leu Ser Pro Gly Asp Val  
 1 5

## 【0115】

<210> 50  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence  
 <220>  
 <223> Description of Artificial Sequence: primer  
 <400> 50

caaacctgag cgcgggcgat gtggc

25

## 【0116】

<210>; 51  
 <211>; 25  
 <212>; DNA  
 <213>; Artificial Sequence  
 <220>;  
 <223>; Description of Artificial Sequence:primer  
 <400>; 51  
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25

## 【0117】

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 <212>; PRT  
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 <220>;  
 <223>; Description of Artificial Sequence: partial amino  
 acid sequence around mutation  
 <400>; 52  
 Asn Leu Ser Ala Gly Asp Val  
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## 【0118】

<210>; 53  
 <211>; 25  
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 <400>; 53  
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25

## 【0119】

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 <211>; 25  
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 <220>;  
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 <400>; 54  
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25

## 【0120】

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 <211>; 7  
 <212>; PRT  
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 <220>;  
 <223>; Description of Artificial Sequence: partial amino  
 acid sequence around mutation  
 <400>; 55  
 Asn Leu Ser Asn Gly Asp Val  
 1 5



## 【0121】

<;210>; 56  
 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
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 <;223>; Description of Artificial Sequence:primer  
 <;400>; 56  
 caaacctgag cggtagcgat gtggc

25

## 【0122】

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 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
 <;220>;  
 <;223>; Description of Artificial Sequence:primer  
 <;400>; 57  
 gtttgactc gccaccgcta caccg

25

## 【0123】

<;210>; 58  
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 <;212>; PRT  
 <;213>; Artificial Sequence  
 <;220>;  
 <;223>; Description of Artificial Sequence: partial amino  
                   acid sequence around mutation  
 <;400>; 58  
 Asn Leu Ser Gly Gly Asp Val  
       1                  5

## 【0124】

<;210>; 59  
 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
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 <;223>; Description of Artificial Sequence:primer  
 <;400>; 59  
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25

## 【0125】

<;210>; 60  
 <;211>; 25  
 <;212>; DNA  
 <;213>; Artificial Sequence  
 <;220>;  
 <;223>; Description of Artificial Sequence:primer  
 <;400>; 60  
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25

## 【0126】

<;210>; 61

【0127】	<211>; 7 <212>; PRT <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence: partial amino acid sequence around mutation <400>; 61 Asn Leu Ser His Gly Asp Val 1                  5	
【0128】	<210>; 62 <211>; 25 <212>; DNA <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence:primer  <400>; 62 cgaaaccgga ttgtactac ctcaa	25
【0129】	<210>; 63 <211>; 25 <212>; DNA <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence:primer <400>; 63 gctttgcct aaccatgatg gagtt	25
【0130】	<210>; 64 <211>; 7 <212>; PRT <213>; Artificial Sequence <220>; <223>; Description of Artificial Sequence: partial amino acid sequence around mutation <400>; 64 Lys Pro Asp Trp Tyr Tyr Leu 1                  5	
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```

【図面の簡単な説明】

【図1】ホスファターゼ活性あるいはリン酸基転移活性を有する活性部位の構成要素となる5つのアミノ酸残基と、これらの空間的位置関係をC $\alpha$ 原子間の距離として示した図である。

【図2】EB-A-Pのアミノ酸配列を、モルガネラ・モルガニ、サルモネラ・チフィリウム、ザイモナス・モビリス由来酸性ホスファターゼのアミノ酸配列とアラインメントした図である。

【図3】EB-AP反応中間体アナログとイノシンの結合様式モデルの結晶構造を示すコンピューターグラフィックス(CG)の写真である。

【図4】EB-APの6量体分子の結晶構造を示すCGの写真である。

【図5】EB-A Pのサブユニットの結晶構造を示すC Gの写真である。

【図6】 EB-A Pの活性部位構造を示す図である。

【図7】部位特異的突然変異誘発法に使用したプライマーセットを示す図である。

【図8】部位特異的突然変異誘発法に使用したプライマーセットを示す図である。

【図9】EB-Apとエンテロバクター・アエロゲネス由来酸性ホスファターゼ(EA-Ap)のアミノ酸配列アラインメントをプログラムBLASTにより行った結果を示す図である。

【図10】EB-APの構造の結晶学データ（1）を示す図である。

【図11】EB-APの構造の結晶学データ(2)を示す図である。

【図12】EB-A Pの構造の結晶学データ(3)を示す図である。

【図13】EB-APの構造の結晶学データ(4)を示す図である。

【図14】EB-APの構造の結晶学データ(5)を示す図である。

【図15】EB-APの構造の結晶学データ(6)を示す図である。

【図16】EB-APの構造の結晶学データ（7）を示す図である。

【図17】EB-APの構造の結晶学データ(8)を示す図である。

【図18】EB-APの構造の結晶学データ(9)を示す図である。

【図19】EB-APの構造の結晶学データ(10)を示す図である。

【図20】EB-A Pの構造の結晶学データ(11)を示す図である。

【図21】EB-APの構造の結晶学データ(12)を示す図である。

【図 2 2】EB-AP の構造の結晶学データ (13) を示す図である。

【図23】EB-APの構造の結晶学データ(14)を示す図である。

【図 2 4】EB-A P の構造の結晶学データ (15) を示す図である。

【図25】EB-APの構造の結晶学データ(16)を示す図である。

【図26】EB-A Pの構造の結晶学データ(17)を示す図である。

【図27】EB-APの構造の結晶学データ(18)を示す図である。

【図28】EB-A Pの構造の結晶学データ（19）を示す図である。

【図29】EB-APの構造の結晶学データ(20)を示す図である。

【図30】EB-APの構造の結晶学データ(21)を示す図である。

【図3 1】EB-A Pの構造の結晶学データ（22）を示す図である。

【図32】EB-A Pの構造の結晶学データ(23)を示す図である。

【図 3 3】EB-APの構造の結晶学データ(24)を示す図である。

【図34】EB-APの構造の結晶学データ(25)を

示す図である。

【図35】EB-APの構造の結晶学データ(26)を示す図である。

【図36】EB-APの構造の結晶学データ(27)を示す図である。

【図37】EB-APの構造の結晶学データ(28)を示す図である。

【図38】EB-APの構造の結晶学データ(29)を示す図である。

【図39】EB-APの構造の結晶学データ(30)を示す図である。

【図40】EB-APの構造の結晶学データ(31)を示す図である。

【図41】EB-APの構造の結晶学データ(32)を示す図である。

【図42】EB-APの構造の結晶学データ(33)を示す図である。

【図43】EB-APの構造の結晶学データ(34)を示す図である。

【図44】EB-APの構造の結晶学データ(35)を示す図である。

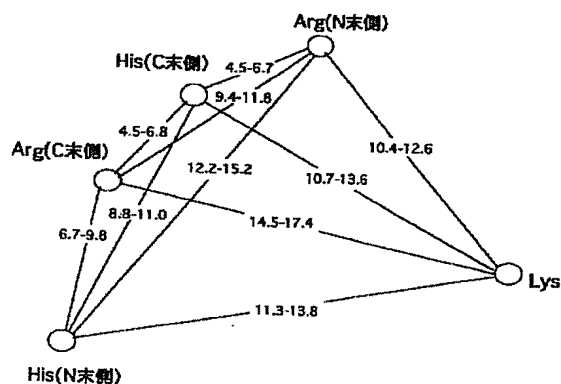
【図45】EB-APの構造の結晶学データ(36)を示す図である。

【図46】部位特異的突然変異誘発法に使用したプライマーセットを示す図である。

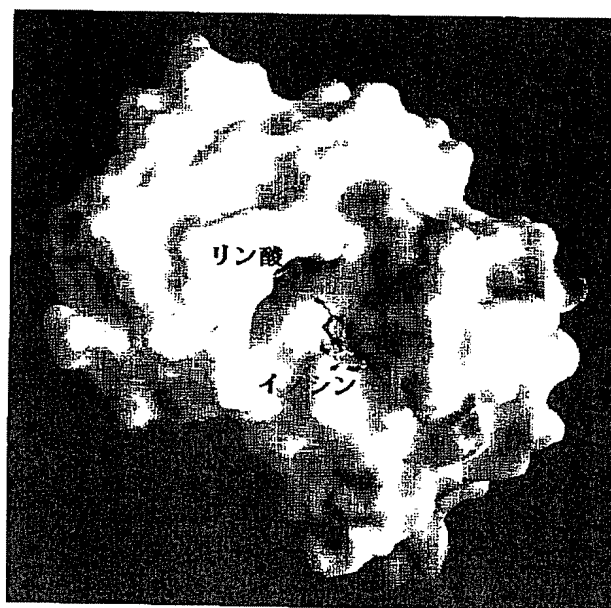
【図47】部位特異的突然変異誘発法に使用したプライマーセットを示す図である。

【図48】部位特異的突然変異誘発法に使用したプライマーセットを示す図である。

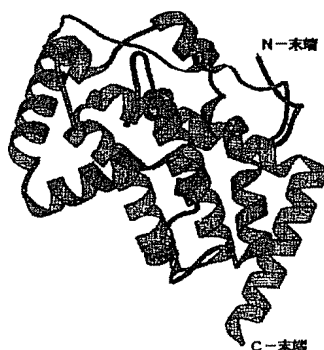
【図1】



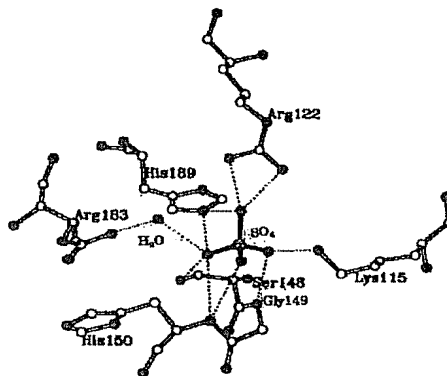
【図3】



【図5】



【図6】



*E. blattae* : LAIVATGNDT TTKPDLYYLK NSEAINSLAL LPPPPAVGSI AFLNDQAMVE QGRLRNTER GKLAEDANL 70  
*M. morgani* : AIPAGNDA TTKPDLYYLK NEQAIDSLKL LPPPEVSGSI QFLNDQAMVE KGRMLRNTER GKQAOADADL  
*S. typhimurium* : KYT SAETVQPFBS PEESVNSQFY LPPPPGNDGP AYRYDKEAYF KGVAILGSPR WKQAAEDADV  
*S. mobilis* : ASGLSQSVSA HTEKSEPSST YEFESDPLLY LAPPTSGSP LQAHDDQTFN STRQLKSTR WALATQDADL \* \*\*

α1 α2 α3

*E. blattae* : SSGGVANAFS GAFGSPITEK DAPALHKILT NMIEDAGDLA TRSAKDRHYMR IRPFAYGVGS TCNTTEQDKL 140  
*M. morgani* : AAGGVATAFS GAFGYPITEK DPELYKLILT NMIEDAGDLA TRSAKREHYMR IRPFAYGTE TCNTKDQKKL  
*S. typhimurium* : SVENIARIFS PVVGAKINPK DTPETWNMLK NLTWTGGYYA TASAKEYMR TRPFVLFNHS TCRPEDENTL  
*S. mobilis* : HIASVLKDYA CAAGMNLIDIA QLPHLANLIK RALRTEYDDI GR-AKNMNR IRPFVDTQDP ICTEKDREGL \* \*\*

α4 α5 α6 α7 α8 α9 α10 α11 α12

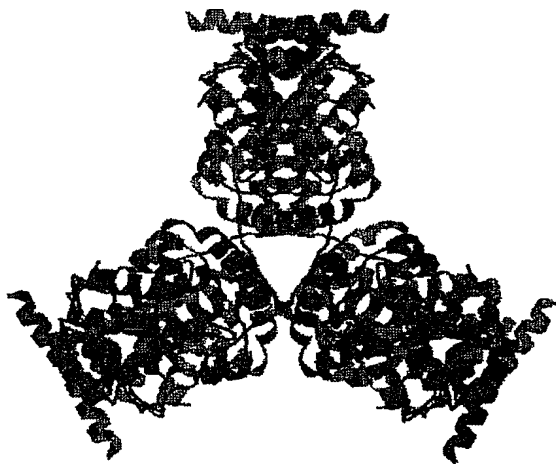
*E. blattae* : SKNGSYPSGH TSIGWATALV LAEINPORON EILKRGYELG QSRVICGYHW QSDYDAARV GSAVATLET 210  
*M. morgani* : STNGSYPSGH TSIGWATALV LAEVPANQD AILKRGYQLG QSRVICGYHW QSDYDAARIV GSAAVATLHS  
*S. typhimurium* : RKNGSYPSGH TAYGTLIALV LSEARPERAQ ELARRGWEEFG QSRVICGAHW QSDVDAGRYV GAVEFARLOT  
*S. mobilis* : GKOGSYPSGH TTIGWSVALI LAELIPDEAA NILORGQIFG TSIRVICGAHW FSDVOAGYIM ASGETAALHG \* \*\*

α13

*E. blattae* : NPAFOOQLOK AKAEFAQHOK K  
*M. morgani* : DPAFOAQLAK AKQFAQKSQ K  
*S. typhimurium* : IPAFOKSLAK VREELNDRNN ILSKEDHPKL NY  
*S. mobilis* : DADFRRMEL ARKELEKART SAHTPDDLLC KIEQSAR \*



【図4】



【図7】

S72F(s) 5'-CA-AAC-CTG-AGC-TTT-GGC-GAT-GTG-GC-3'  
 S72F(as) 3'-GT-TTG-GAC-TCG-AAA-CCG-CTA-CAC-CG-5'  
           N L S F72 G D V  
 S72Y(s) 5'-CA-AAC-CTG-AGC-TAC-GGC-GAT-GTG-GC-3'  
 S72Y(as) 3'-GT-TTG-GAC-TCG-ATG-CCG-CTA-CAC-CG-5'  
           N L S Y72 G D V  
 S72W(s) 5'-CA-AAC-CTG-AGC-TGG-GGC-GAT-GTG-GC-3'  
 S72W(as) 3'-GT-TTG-GAC-TCG-ACC-CCG-CTA-CAC-CG-5'  
           N L S W72 G D V  
 S72D(s) 5'-CA-AAC-CTG-AGC-GAC-GGC-GAT-GTG-GC-3'  
 S72D(as) 3'-GT-TTG-GAC-TCG-CTG-CCG-CTA-CAC-CG-5'  
           N L S D72 G D V  
 S72V(s) 5'-CA-AAC-CTG-AGC-GTT-GGC-GAT-GTG-GC-3'  
 S72V(as) 3'-GT-TTG-GAC-TCG-CAA-CCG-CTA-CAC-CG-5'  
           N L S V72 G D V  
 S72E(s) 5'-CA-AAC-CTG-AGC-GAA-GGC-GAT-GTG-GC-3'  
 S72E(as) 3'-GT-TTG-GAC-TCG-CYT-CCG-CTA-CAC-CG-5'  
           N L S E72 G D V  
 S72M(s) 5'-CA-AAC-CTG-AGC-ATG-GGC-GAT-GTG-GC-3'  
 S72M(as) 3'-GT-TTG-GAC-TCG-TAC-CCG-CTA-CAC-CG-5'  
           N L S M72 G D V  
 S72T(s) 5'-CA-AAC-CTG-AGC-ACC-GGC-GAT-GTG-GC-3'  
 S72T(as) 3'-GT-TTG-GAC-TCG-TGG-CCG-CTA-CAC-CG-5'  
           N L S T72 G D V  
 S72L(s) 5'-CA-AAC-CTG-AGC-CTG-GGC-GAT-GTG-GC-3'  
 S72L(as) 3'-GT-TTG-GAC-TCG-GAC-CCG-CTA-CAC-CG-5'  
           N L S L72 G D V  
 S72R(s) 5'-CA-AAC-CTG-AGC-CGT-GGC-GAT-GTG-GC-3'  
 S72R(as) 3'-GT-TTG-GAC-TCG-GCA-CCG-CTA-CAC-CG-5'  
           N L S R72 G D V  
 S72Q(s) 5'-CA-AAC-CTG-AGC-CAG-GGC-GAT-GTG-GC-3'  
 S72Q(as) 3'-GT-TTG-GAC-TCG-GTC-CCG-CTA-CAC-CG-5'  
           N L S Q72 G D V  
 S72K(s) 5'-CA-AAC-CTG-AGC-AAA-GGC-GAT-GTG-GC-3'  
 S72K(as) 3'-GT-TTG-GAC-TCG-TTT-CCG-CTA-CAC-CG-5'  
           N L S K72 G D V  
 S72P(s) 5'-CA-AAC-CTG-AGC-CCG-GGC-GAT-GTG-GC-3'  
 S72P(as) 3'-GT-TTG-GAC-TCG-GGC-CCG-CTA-CAC-CG-5'  
           N L S P72 G D V  
 S72A(s) 5'-CA-AAC-CTG-AGC-GCG-GGC-GAT-GTG-GC-3'  
 S72A(as) 3'-GT-TTG-GAC-TCG-CGC-CCG-CTA-CAC-CG-5'  
           N L S A72 G D V  
 S72N(s) 5'-CA-AAC-CTG-AGC-AAC-GGC-GAT-GTG-GC-3'  
 S72N(as) 3'-GT-TTG-GAC-TCG-TTG-CCG-CTA-CAC-CG-5'  
           N L S N72 G D V  
 S72G(s) 5'-CA-AAC-CTG-AGC-GGT-GGC-GAT-GTG-GC-3'  
 S72G(as) 3'-GT-TTG-GAC-TCG-CCA-CCG-CTA-CAC-CG-5'  
           N L S G72 G D V  
 S72H(s) 5'-CA-AAC-CTG-AGC-CAC-GGC-GAT-GTG-GC-3'  
 S72H(as) 3'-GT-TTG-GAC-TCG-GTG-CCG-CTA-CAC-CG-5'  
           N L S H72 G D V

## 【図8】

**L16W(s)**     5'-CG-AAA-CCG-GAT-TGG-TAC-TAC-CTC-AA-3'  
**L16W(as)**    3'-GC-TTT-GGC-CTA-ACC-ATG-ATG-GAG-TT-5'  
                  K     P     D     W16 Y     Y     L

**S71W(s)**     5'-AT-GCA-AAC-CTG-TGG-AGT-GGC-GAT-GT-3'  
**S71W(as)**    3'-TA-CGT-TTG-GAC-ACC-TCA-CCG-CTA-CA-5'  
                  A     N     L     W71 S     G     D

**G73W(s)**     5'-AC-CTG-AGC-AGT-TGG-GAT-GTG-GCG-AA-3'  
**G73W(as)**    3'-TG-GAC-TCG-TCA-ACC-CTA-CAC-CGC-TT-5'  
                  L     S     S     W73 D     V     A

**E104F(s)**     5'-CC-AAT-ATG-ATT-TTT-GAC-GCC-GGG-GA-3'  
**E104F(as)**    3'-GG-TTA-TAC-TAA-AAA-CTG-CGG-CCC-CT-5'  
                  N     M     I     F104 D     A     G

**E104W(s)**     5'-CC-AAT-ATG-ATT-TGG-GAC-GCC-GGG-GA-3'  
**E104W(as)**    3'-GG-TTA-TAC-TAA-ACC-CTG-CGG-CCC-CT-5'  
                  N     M     I     W104 D     A     G

## 【図9】

EB-AP:     LALVATGNDTTTKPDLYYLKNSEAINSLALLPPPPAVGSIAFLNDQAMYEQGRLLRNTER  
                  V   GND TTKPDLYYLKN++AI+SLALLPPPP VGSI AFLNDQAMYE+GRLLRNTER  
 EA-AP:     LVPAGNDATTKPDLYYLKNAQAIDSLALLPPPPPEVGSIAFLNDQAMYEGRLLRNTER

[72]

EB-AP:     GKLAEDANLSSGGVANAFSGAFGSPITEKDAPALHKLLTNMIEDAGDLATRSKDHMYR  
                  GKLAEDANLS+GGVANAFS AFGSPITEKDAP LHKLLTNMIEDAGDLATRSK+ YMR  
 EA-AP:     GKLAEDANLSAGGVANAFSSAFGSPITEKDAPQLHKLLTNMIEDAGDLATRSKEKMYR

[70]

EB-AP:     IRPFAFYGVSTCNTTEQDKLSKNGSYPSGHTSIGWATALVLAIEINPQRQNEILKRGYELG  
                  IRPFAFYGVSTCNTTEQDKLSKNGSYPSGHTSIGWATALVLAIEINPQRQNEILKRGYELG  
 EA-AP:     IRPFAFYGVSTCNTTEQDKLSKNGSYPSGHTSIGWATALVLAIEINPQRQNEILKRGYELG

EB-AP:     QSRVICGYHWQSDVDAARVVGSAVVATLHTNPAFQQQLQKAKAEFAQHOKK  
                  +SRVICGYHWQSDVDAAR+VGS AVVATLHTNPAFQQQLQKAK EFA+ QK  
 EA-AP:     ESRVICGYHWQSDVDAARIVGS AVVATLHTNPAFQQQLQKAKDEFKTOK

【図10】

ATOM	1	N	GLY	A	7	35.965	71.208	89.712	1.00	36.57
ATOM	2	CA	GLY	A	7	37.459	71.295	89.574	1.00	31.92
ATOM	3	C	GLY	A	7	38.160	69.982	89.872	1.00	29.76
ATOM	4	O	GLY	A	7	39.301	69.858	89.492	1.00	31.81
ATOM	5	N	ASN	A	8	37.485	68.990	90.532	1.00	26.40
ATOM	6	CA	ASN	A	8	38.284	67.775	90.697	1.00	26.63
ATOM	7	C	ASN	A	8	38.466	67.018	89.396	1.00	29.21
ATOM	8	O	ASN	A	8	37.736	67.238	88.431	1.00	30.52
ATOM	9	CB	ASN	A	8	37.677	66.810	91.702	1.00	27.01
ATOM	10	CG	ASN	A	8	37.725	67.396	93.104	1.00	32.45
ATOM	11	OD1	ASN	A	8	38.751	67.744	93.636	1.00	30.02
ATOM	12	ND2	ASN	A	8	36.545	67.536	93.707	1.00	31.60
ATOM	13	N	ASP	A	9	39.455	66.154	89.463	1.00	29.14
ATOM	14	CA	ASP	A	9	39.787	65.216	88.391	1.00	30.47
ATOM	15	C	ASP	A	9	40.661	64.081	88.901	1.00	31.02
ATOM	16	O	ASP	A	9	40.804	63.931	90.110	1.00	31.00
ATOM	17	CB	ASP	A	9	40.394	65.960	87.195	1.00	30.92
ATOM	18	CG	ASP	A	9	41.802	66.484	87.429	1.00	32.66
ATOM	19	OD1	ASP	A	9	42.307	66.333	88.532	1.00	35.03
ATOM	20	OD2	ASP	A	9	42.400	67.018	86.493	1.00	31.63
ATOM	21	N	THR	A	10	41.272	63.298	87.998	1.00	28.72
ATOM	22	CA	THR	A	10	42.188	62.228	88.430	1.00	28.53
ATOM	23	C	THR	A	10	43.408	62.655	89.259	1.00	30.10
ATOM	24	O	THR	A	10	43.946	61.944	90.095	1.00	29.06
ATOM	25	CB	THR	A	10	42.692	61.405	87.235	1.00	26.05
ATOM	26	OG1	THR	A	10	43.272	60.172	87.655	1.00	27.75
ATOM	27	CG2	THR	A	10	43.670	62.174	86.313	1.00	23.76
ATOM	28	N	THR	A	11	43.814	63.900	88.996	1.00	30.82
ATOM	29	CA	THR	A	11	44.932	64.389	89.799	1.00	32.79
ATOM	30	C	THR	A	11	44.605	64.736	91.267	1.00	36.32
ATOM	31	O	THR	A	11	45.435	64.658	92.162	1.00	37.21
ATOM	32	CB	THR	A	11	45.588	65.591	89.143	1.00	30.53
ATOM	33	OG1	THR	A	11	44.845	66.781	89.359	1.00	27.79
ATOM	34	CG2	THR	A	11	45.899	65.362	87.656	1.00	32.16
ATOM	35	N	THR	A	12	43.317	65.076	91.495	1.00	34.81
ATOM	36	CA	THR	A	12	42.910	65.213	92.900	1.00	32.91
ATOM	37	C	THR	A	12	42.265	63.992	93.549	1.00	33.08
ATOM	38	O	THR	A	12	42.350	63.742	94.736	1.00	32.49
ATOM	39	CB	THR	A	12	41.963	66.395	93.077	1.00	30.92
ATOM	40	OG1	THR	A	12	40.719	66.162	92.409	1.00	32.04
ATOM	41	CG2	THR	A	12	42.599	67.667	92.543	1.00	29.75
ATOM	42	N	LYS	A	13	41.565	63.229	92.703	1.00	31.17
ATOM	43	CA	LYS	A	13	40.791	62.064	93.174	1.00	30.27
ATOM	44	C	LYS	A	13	40.904	60.812	92.287	1.00	31.40
ATOM	45	O	LYS	A	13	39.981	60.348	91.605	1.00	33.05
ATOM	46	CB	LYS	A	13	39.294	62.395	93.331	1.00	29.09
ATOM	47	CG	LYS	A	13	39.001	63.747	93.965	1.00	32.97
ATOM	48	CD	LYS	A	13	37.536	64.076	94.166	1.00	37.86
ATOM	49	CE	LYS	A	13	36.767	62.909	94.772	1.00	47.28
ATOM	50	NZ	LYS	A	13	35.340	63.270	94.947	1.00	52.08
ATOM	51	N	PRO	A	14	42.138	60.283	92.279	1.00	33.01
ATOM	52	CA	PRO	A	14	42.516	59.249	91.290	1.00	32.06
ATOM	53	C	PRO	A	14	41.823	57.907	91.452	1.00	30.98
ATOM	54	O	PRO	A	14	41.961	56.989	90.668	1.00	32.57

【図11】

ATOM	55	CB	PRO	A	14	44.035	59.145	91.468	1.00	34.46
ATOM	56	CG	PRO	A	14	44.283	59.564	92.920	1.00	33.02
ATOM	57	CD	PRO	A	14	43.225	60.638	93.181	1.00	34.46
ATOM	58	N	ASP	A	15	41.046	57.815	92.513	1.00	29.27
ATOM	59	CA	ASP	A	15	40.204	56.655	92.809	1.00	28.89
ATOM	60	C	ASP	A	15	38.810	56.684	92.146	1.00	21.76
ATOM	61	O	ASP	A	15	38.078	55.706	92.030	1.00	20.59
ATOM	62	CB	ASP	A	15	40.125	56.599	94.368	1.00	37.60
ATOM	63	CG	ASP	A	15	39.589	57.903	95.080	1.00	45.11
ATOM	64	OD1	ASP	A	15	40.062	59.044	94.817	1.00	45.67
ATOM	65	OD2	ASP	A	15	38.687	57.751	95.922	1.00	49.07
ATOM	66	N	LEU	A	16	38.495	57.910	91.726	1.00	20.49
ATOM	67	CA	LEU	A	16	37.182	58.179	91.135	1.00	23.90
ATOM	68	C	LEU	A	16	37.156	58.814	89.727	1.00	22.23
ATOM	69	O	LEU	A	16	36.109	59.011	89.134	1.00	23.21
ATOM	70	CB	LEU	A	16	36.354	59.099	92.029	1.00	23.35
ATOM	71	CG	LEU	A	16	35.814	58.432	93.297	1.00	25.48
ATOM	72	CD1	LEU	A	16	34.876	57.253	93.075	1.00	24.05
ATOM	73	CD2	LEU	A	16	35.092	59.477	94.104	1.00	25.22
ATOM	74	N	TYR	A	17	38.343	59.175	89.273	1.00	20.96
ATOM	75	CA	TYR	A	17	38.555	59.605	87.889	1.00	22.04
ATOM	76	C	TYR	A	17	39.780	58.903	87.334	1.00	22.80
ATOM	77	O	TYR	A	17	40.790	58.799	88.021	1.00	23.48
ATOM	78	CB	TYR	A	17	38.856	61.095	87.711	1.00	18.01
ATOM	79	CG	TYR	A	17	37.928	62.099	88.371	1.00	24.78
ATOM	80	CD1	TYR	A	17	37.129	62.916	87.542	1.00	22.78
ATOM	81	CD2	TYR	A	17	37.905	62.248	89.781	1.00	23.58
ATOM	82	CE1	TYR	A	17	36.317	63.919	88.113	1.00	26.51
ATOM	83	CE2	TYR	A	17	37.090	63.240	90.349	1.00	22.88
ATOM	84	CZ	TYR	A	17	36.303	64.059	89.517	1.00	24.63
ATOM	85	OH	TYR	A	17	35.482	65.023	90.066	1.00	22.92
ATOM	86	N	TYR	A	18	39.670	58.482	86.053	1.00	26.17
ATOM	87	CA	TYR	A	18	40.838	58.209	85.191	1.00	21.13
ATOM	88	C	TYR	A	18	41.332	59.414	84.464	1.00	19.92
ATOM	89	O	TYR	A	18	42.490	59.511	84.083	1.00	22.64
ATOM	90	CB	TYR	A	18	40.563	57.195	84.080	1.00	17.53
ATOM	91	CG	TYR	A	18	40.312	55.826	84.610	1.00	16.91
ATOM	92	CD1	TYR	A	18	41.425	55.028	84.916	1.00	19.86
ATOM	93	CD2	TYR	A	18	38.985	55.372	84.771	1.00	16.65
ATOM	94	CE1	TYR	A	18	41.218	53.725	85.383	1.00	18.64
ATOM	95	CE2	TYR	A	18	38.765	54.053	85.213	1.00	17.52
ATOM	96	CZ	TYR	A	18	39.892	53.262	85.515	1.00	21.18
ATOM	97	OH	TYR	A	18	39.734	51.974	85.977	1.00	26.15
ATOM	98	N	LEU	A	19	40.412	60.336	84.236	1.00	21.49
ATOM	99	CA	LEU	A	19	40.788	61.462	83.366	1.00	22.71
ATOM	100	C	LEU	A	19	41.094	62.812	84.021	1.00	25.01
ATOM	101	O	LEU	A	19	40.771	63.125	85.159	1.00	25.24
ATOM	102	CB	LEU	A	19	39.708	61.669	82.290	1.00	21.68
ATOM	103	CG	LEU	A	19	39.301	60.442	81.432	1.00	22.88
ATOM	104	CD1	LEU	A	19	40.430	59.842	80.583	1.00	20.39
ATOM	105	CD2	LEU	A	19	38.078	60.812	80.608	1.00	18.83
ATOM	106	N	LYS	A	20	41.736	63.667	83.246	1.00	26.44
ATOM	107	CA	LYS	A	20	41.947	65.032	83.717	1.00	26.77
ATOM	108	C	LYS	A	20	40.935	66.034	83.292	1.00	26.42

【図12】

ATOM	109	O	LYS	A	20	40.182	65.870	82.341	1.00	29.05
ATOM	110	CB	LYS	A	20	43.239	65.608	83.187	1.00	30.61
ATOM	111	CG	LYS	A	20	44.400	64.791	83.648	1.00	32.90
ATOM	112	CD	LYS	A	20	45.633	65.326	82.963	1.00	39.72
ATOM	113	CE	LYS	A	20	46.698	64.259	83.113	1.00	50.27
ATOM	114	NZ	LYS	A	20	46.148	62.977	82.610	1.00	62.00
ATOM	115	N	ASN	A	21	41.050	67.184	83.943	1.00	24.09
ATOM	116	CA	ASN	A	21	40.154	68.246	83.530	1.00	23.98
ATOM	117	C	ASN	A	21	40.177	68.539	82.032	1.00	25.08
ATOM	118	O	ASN	A	21	39.134	68.722	81.427	1.00	25.36
ATOM	119	CB	ASN	A	21	40.310	69.512	84.371	1.00	23.81
ATOM	120	CG	ASN	A	21	39.601	69.311	85.697	1.00	26.97
ATOM	121	OD1	ASN	A	21	38.392	69.175	85.836	1.00	26.36
ATOM	122	ND2	ASN	A	21	40.403	69.303	86.744	1.00	32.00
ATOM	123	N	SER	A	22	41.378	68.486	81.450	1.00	23.72
ATOM	124	CA	SER	A	22	41.592	68.804	80.008	1.00	25.53
ATOM	125	C	SER	A	22	40.992	67.752	79.068	1.00	25.77
ATOM	126	O	SER	A	22	40.524	68.007	77.966	1.00	27.65
ATOM	127	CB	SER	A	22	43.079	68.868	79.699	1.00	23.34
ATOM	128	OG	SER	A	22	43.719	67.716	80.303	1.00	33.30
ATOM	129	N	GLU	A	23	40.957	66.529	79.624	1.00	22.35
ATOM	130	CA	GLU	A	23	40.320	65.466	78.899	1.00	21.87
ATOM	131	C	GLU	A	23	38.811	65.375	78.974	1.00	23.18
ATOM	132	O	GLU	A	23	38.197	64.451	78.471	1.00	25.83
ATOM	133	CB	GLU	A	23	40.923	64.165	79.337	1.00	22.13
ATOM	134	CG	GLU	A	23	42.451	64.215	79.214	1.00	26.78
ATOM	135	CD	GLU	A	23	43.021	62.908	79.718	1.00	30.40
ATOM	136	OE1	GLU	A	23	42.946	62.648	80.900	1.00	31.10
ATOM	137	OE2	GLU	A	23	43.544	62.118	78.957	1.00	32.35
ATOM	138	N	ALA	A	24	38.196	66.359	79.610	1.00	21.49
ATOM	139	CA	ALA	A	24	36.751	66.165	79.738	1.00	22.48
ATOM	140	C	ALA	A	24	35.973	66.420	78.438	1.00	22.81
ATOM	141	O	ALA	A	24	36.325	67.333	77.704	1.00	23.36
ATOM	142	CB	ALA	A	24	36.188	67.183	80.734	1.00	21.43
ATOM	143	N	ILE	A	25	34.859	65.694	78.228	1.00	23.46
ATOM	144	CA	ILE	A	25	33.845	66.149	77.243	1.00	23.60
ATOM	145	C	ILE	A	25	33.312	67.535	77.530	1.00	24.71
ATOM	146	O	ILE	A	25	32.788	67.809	78.603	1.00	25.03
ATOM	147	CB	ILE	A	25	32.684	65.160	77.096	1.00	20.26
ATOM	148	CG1	ILE	A	25	33.237	63.749	76.838	1.00	23.14
ATOM	149	CG2	ILE	A	25	31.739	65.555	75.954	1.00	21.26
ATOM	150	CD1	ILE	A	25	34.298	63.551	75.722	1.00	16.94
ATOM	151	N	ASN	A	26	33.485	68.431	76.562	1.00	22.50
ATOM	152	CA	ASN	A	26	32.797	69.706	76.751	1.00	22.04
ATOM	153	C	ASN	A	26	31.295	69.680	76.533	1.00	22.52
ATOM	154	O	ASN	A	26	30.731	70.042	75.509	1.00	22.34
ATOM	155	CB	ASN	A	26	33.474	70.744	75.900	1.00	20.15
ATOM	156	CG	ASN	A	26	32.982	72.133	76.217	1.00	24.94
ATOM	157	OD1	ASN	A	26	31.923	72.459	76.732	1.00	29.46
ATOM	158	ND2	ASN	A	26	33.827	73.032	75.809	1.00	25.76
ATOM	159	N	SER	A	27	30.627	69.289	77.622	1.00	19.77
ATOM	160	CA	SER	A	27	29.166	69.168	77.549	1.00	18.88
ATOM	161	C	SER	A	27	28.412	70.423	77.177	1.00	18.74
ATOM	162	O	SER	A	27	27.390	70.393	76.517	1.00	21.73

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ATOM	163	CB	SER	A	27	28.606	68.619	78.870	1.00	19.35
ATOM	164	OG	SER	A	27	28.967	69.518	79.940	1.00	19.36
ATOM	165	N	LEU	A	28	28.961	71.564	77.588	1.00	18.08
ATOM	166	CA	LEU	A	28	28.271	72.815	77.262	1.00	20.15
ATOM	167	C	LEU	A	28	28.283	73.062	75.761	1.00	23.12
ATOM	168	O	LEU	A	28	27.303	73.485	75.165	1.00	22.25
ATOM	169	CB	LEU	A	28	28.990	74.042	77.798	1.00	17.00
ATOM	170	CG	LEU	A	28	28.159	75.188	78.376	1.00	18.01
ATOM	171	CD1	LEU	A	28	26.847	75.547	77.733	1.00	14.28
ATOM	172	CD2	LEU	A	28	29.053	76.394	78.592	1.00	16.45
ATOM	173	N	ALA	A	29	29.478	72.767	75.193	1.00	23.87
ATOM	174	CA	ALA	A	29	29.598	72.827	73.707	1.00	22.62
ATOM	175	C	ALA	A	29	28.773	71.847	72.837	1.00	20.86
ATOM	176	O	ALA	A	29	28.192	72.239	71.830	1.00	25.89
ATOM	177	CB	ALA	A	29	31.065	72.692	73.326	1.00	20.24
ATOM	178	N	LEU	A	30	28.733	70.580	73.267	1.00	15.78
ATOM	179	CA	LEU	A	30	28.079	69.497	72.519	1.00	18.05
ATOM	180	C	LEU	A	30	26.557	69.416	72.559	1.00	22.38
ATOM	181	O	LEU	A	30	25.845	69.251	71.566	1.00	23.63
ATOM	182	CB	LEU	A	30	28.732	68.194	72.977	1.00	16.47
ATOM	183	CG	LEU	A	30	28.234	66.887	72.360	1.00	17.59
ATOM	184	CD1	LEU	A	30	28.812	65.706	73.120	1.00	12.95
ATOM	185	CD2	LEU	A	30	28.456	66.775	70.850	1.00	13.89
ATOM	186	N	LEU	A	31	26.075	69.533	73.812	1.00	22.39
ATOM	187	CA	LEU	A	31	24.633	69.430	74.049	1.00	18.84
ATOM	188	C	LEU	A	31	23.817	70.624	73.538	1.00	16.30
ATOM	189	O	LEU	A	31	24.260	71.763	73.576	1.00	19.93
ATOM	190	CB	LEU	A	31	24.381	69.199	75.556	1.00	16.94
ATOM	191	CG	LEU	A	31	24.923	67.873	76.095	1.00	17.95
ATOM	192	CD1	LEU	A	31	24.177	66.669	75.553	1.00	11.60
ATOM	193	CD2	LEU	A	31	24.823	67.878	77.628	1.00	18.77
ATOM	194	N	PRO	A	32	22.581	70.333	73.105	1.00	14.80
ATOM	195	CA	PRO	A	32	21.589	71.404	72.910	1.00	18.31
ATOM	196	C	PRO	A	32	21.228	72.028	74.278	1.00	22.24
ATOM	197	O	PRO	A	32	21.453	71.442	75.327	1.00	22.27
ATOM	198	CB	PRO	A	32	20.402	70.621	72.348	1.00	15.94
ATOM	199	CG	PRO	A	32	20.545	69.184	72.847	1.00	16.93
ATOM	200	CD	PRO	A	32	22.038	68.972	72.954	1.00	15.56
ATOM	201	N	PRO	A	33	20.657	73.249	74.287	1.00	23.41
ATOM	202	CA	PRO	A	33	20.190	73.780	75.586	1.00	20.34
ATOM	203	C	PRO	A	33	19.059	72.945	76.084	1.00	19.93
ATOM	204	O	PRO	A	33	18.409	72.292	75.285	1.00	18.67
ATOM	205	CB	PRO	A	33	19.659	75.158	75.224	1.00	18.52
ATOM	206	CG	PRO	A	33	20.267	75.499	73.877	1.00	21.71
ATOM	207	CD	PRO	A	33	20.406	74.146	73.177	1.00	21.12
ATOM	208	N	PRO	A	34	18.785	72.950	77.411	1.00	19.36
ATOM	209	CA	PRO	A	34	17.645	72.138	77.863	1.00	13.70
ATOM	210	C	PRO	A	34	16.348	72.759	77.351	1.00	11.77
ATOM	211	O	PRO	A	34	16.280	73.937	77.090	1.00	14.58
ATOM	212	CB	PRO	A	34	17.760	72.358	79.389	1.00	13.66
ATOM	213	CG	PRO	A	34	18.471	73.698	79.571	1.00	14.81
ATOM	214	CD	PRO	A	34	19.499	73.679	78.464	1.00	16.49
ATOM	215	N	PRO	A	35	15.257	72.007	77.284	1.00	12.52
ATOM	216	CA	PRO	A	35	14.011	72.710	76.973	1.00	13.71

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ATOM	217	C	PRO	A	35	13.665	73.842	77.945	1.00	20.26
ATOM	218	O	PRO	A	35	13.728	73.715	79.159	1.00	20.52
ATOM	219	CB	PRO	A	35	12.997	71.579	76.991	1.00	11.74
ATOM	220	CG	PRO	A	35	13.723	70.243	77.051	1.00	12.04
ATOM	221	CD	PRO	A	35	15.140	70.581	77.482	1.00	11.57
ATOM	222	N	ALA	A	36	13.311	74.962	77.356	1.00	19.25
ATOM	223	CA	ALA	A	36	12.919	76.136	78.122	1.00	18.78
ATOM	224	C	ALA	A	36	11.457	76.120	78.497	1.00	18.25
ATOM	225	O	ALA	A	36	10.582	75.579	77.847	1.00	18.88
ATOM	226	CB	ALA	A	36	13.152	77.414	77.304	1.00	17.95
ATOM	227	N	VAL	A	37	11.182	76.753	79.609	1.00	18.03
ATOM	228	CA	VAL	A	37	9.803	77.005	79.965	1.00	16.78
ATOM	229	C	VAL	A	37	9.135	77.993	78.998	1.00	17.18
ATOM	230	O	VAL	A	37	9.640	79.048	78.650	1.00	19.89
ATOM	231	CB	VAL	A	37	9.740	77.500	81.436	1.00	18.33
ATOM	232	CG1	VAL	A	37	10.381	76.501	82.418	1.00	13.83
ATOM	233	CG2	VAL	A	37	8.300	77.825	81.832	1.00	14.21
ATOM	234	N	GLY	A	38	7.952	77.616	78.561	1.00	18.34
ATOM	235	CA	GLY	A	38	7.422	78.249	77.343	1.00	22.06
ATOM	236	C	GLY	A	38	7.538	77.398	76.043	1.00	21.25
ATOM	237	O	GLY	A	38	6.851	77.623	75.068	1.00	22.09
ATOM	238	N	SER	A	39	8.422	76.401	76.060	1.00	21.73
ATOM	239	CA	SER	A	39	8.520	75.487	74.905	1.00	20.30
ATOM	240	C	SER	A	39	7.604	74.277	74.964	1.00	21.10
ATOM	241	O	SER	A	39	7.217	73.736	76.002	1.00	19.55
ATOM	242	CB	SER	A	39	9.946	74.998	74.748	1.00	15.45
ATOM	243	OG	SER	A	39	10.197	73.967	75.704	1.00	15.38
ATOM	244	N	ILE	A	40	7.287	73.796	73.772	1.00	17.17
ATOM	245	CA	ILE	A	40	6.618	72.485	73.702	1.00	14.71
ATOM	246	C	ILE	A	40	7.475	71.311	74.225	1.00	10.81
ATOM	247	O	ILE	A	40	6.998	70.315	74.782	1.00	15.23
ATOM	248	CB	ILE	A	40	6.102	72.235	72.219	1.00	15.78
ATOM	249	CG1	ILE	A	40	5.162	73.368	71.791	1.00	15.41
ATOM	250	CG2	ILE	A	40	5.406	70.863	72.091	1.00	14.54
ATOM	251	CD1	ILE	A	40	4.812	73.332	70.307	1.00	18.26
ATOM	252	N	ALA	A	41	8.790	71.443	74.040	1.00	10.69
ATOM	253	CA	ALA	A	41	9.633	70.373	74.530	1.00	13.79
ATOM	254	C	ALA	A	41	9.566	70.300	76.091	1.00	15.36
ATOM	255	O	ALA	A	41	9.369	69.245	76.683	1.00	20.02
ATOM	256	CB	ALA	A	41	11.046	70.610	74.065	1.00	11.61
ATOM	257	N	PHE	A	42	9.547	71.495	76.702	1.00	16.94
ATOM	258	CA	PHE	A	42	9.200	71.480	78.151	1.00	15.75
ATOM	259	C	PHE	A	42	7.818	70.970	78.533	1.00	16.07
ATOM	260	O	PHE	A	42	7.652	70.182	79.448	1.00	19.72
ATOM	261	CB	PHE	A	42	9.513	72.819	78.819	1.00	17.93
ATOM	262	CG	PHE	A	42	9.380	72.700	80.338	1.00	20.96
ATOM	263	CD1	PHE	A	42	10.297	71.904	81.056	1.00	19.46
ATOM	264	CD2	PHE	A	42	8.324	73.370	80.997	1.00	20.99
ATOM	265	CE1	PHE	A	42	10.148	71.763	82.450	1.00	17.30
ATOM	266	CE2	PHE	A	42	8.190	73.248	82.402	1.00	19.79
ATOM	267	CZ	PHE	A	42	9.111	72.443	83.100	1.00	13.36
ATOM	268	N	LEU	A	43	6.790	71.375	77.765	1.00	19.00
ATOM	269	CA	LEU	A	43	5.507	70.643	77.917	1.00	19.22
ATOM	270	C	LEU	A	43	5.573	69.103	77.945	1.00	19.39

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ATOM	271	O	LEU	A	43	4.957	68.410	78.749	1.00	17.69
ATOM	272	CB	LEU	A	43	4.472	71.003	76.826	1.00	21.60
ATOM	273	CG	LEU	A	43	3.213	71.850	77.034	1.00	24.67
ATOM	274	CD1	LEU	A	43	2.597	71.800	78.433	1.00	17.68
ATOM	275	CD2	LEU	A	43	2.172	71.549	75.953	1.00	21.72
ATOM	276	N	ASN	A	44	6.392	68.588	77.023	1.00	19.47
ATOM	277	CA	ASN	A	44	6.653	67.176	77.076	1.00	19.82
ATOM	278	C	ASN	A	44	7.419	66.619	78.312	1.00	17.44
ATOM	279	O	ASN	A	44	7.018	65.604	78.855	1.00	15.52
ATOM	280	CB	ASN	A	44	7.259	66.847	75.747	1.00	19.07
ATOM	281	CG	ASN	A	44	7.491	65.366	75.643	1.00	22.97
ATOM	282	OD1	ASN	A	44	8.605	64.906	75.468	1.00	30.35
ATOM	283	ND2	ASN	A	44	6.444	64.588	75.862	1.00	22.13
ATOM	284	N	ASP	A	45	8.482	67.324	78.726	1.00	19.71
ATOM	285	CA	ASP	A	45	9.175	67.050	80.020	1.00	19.87
ATOM	286	C	ASP	A	45	8.192	66.977	81.213	1.00	19.30
ATOM	287	O	ASP	A	45	8.103	66.009	81.956	1.00	21.00
ATOM	288	CB	ASP	A	45	10.225	68.119	80.273	1.00	13.57
ATOM	289	CG	ASP	A	45	11.563	67.769	79.706	1.00	12.64
ATOM	290	OD1	ASP	A	45	12.408	68.656	79.625	1.00	15.68
ATOM	291	OD2	ASP	A	45	11.823	66.611	79.414	1.00	14.57
ATOM	292	N	GLN	A	46	7.347	68.007	81.299	1.00	19.62
ATOM	293	CA	GLN	A	46	6.199	67.904	82.220	1.00	19.44
ATOM	294	C	GLN	A	46	5.259	66.702	82.166	1.00	22.23
ATOM	295	O	GLN	A	46	4.960	66.057	83.175	1.00	21.67
ATOM	296	CB	GLN	A	46	5.353	69.153	82.218	1.00	16.35
ATOM	297	CG	GLN	A	46	6.282	70.333	82.395	1.00	18.35
ATOM	298	CD	GLN	A	46	5.398	71.519	82.591	1.00	26.07
ATOM	299	OE1	GLN	A	46	5.334	72.143	83.629	1.00	31.83
ATOM	300	NE2	GLN	A	46	4.622	71.823	81.591	1.00	22.82
ATOM	301	N	ALA	A	47	4.838	66.364	80.935	1.00	19.12
ATOM	302	CA	ALA	A	47	3.979	65.187	80.813	1.00	17.83
ATOM	303	C	ALA	A	47	4.661	63.871	81.172	1.00	15.90
ATOM	304	O	ALA	A	47	4.065	62.940	81.701	1.00	18.55
ATOM	305	CB	ALA	A	47	3.441	65.066	79.367	1.00	17.11
ATOM	306	N	MET	A	48	5.970	63.818	80.841	1.00	18.16
ATOM	307	CA	MET	A	48	6.799	62.644	81.235	1.00	19.52
ATOM	308	C	MET	A	48	7.012	62.460	82.765	1.00	21.38
ATOM	309	O	MET	A	48	6.996	61.358	83.316	1.00	20.83
ATOM	310	CB	MET	A	48	8.173	62.667	80.539	1.00	21.42
ATOM	311	CG	MET	A	48	8.150	62.603	78.984	1.00	29.81
ATOM	312	SD	MET	A	48	7.330	61.126	78.308	1.00	36.20
ATOM	313	CE	MET	A	48	5.582	61.633	78.280	1.00	33.60
ATOM	314	N	TYR	A	49	7.139	63.655	83.414	1.00	21.32
ATOM	315	CA	TYR	A	49	7.066	63.807	84.885	1.00	21.30
ATOM	316	C	TYR	A	49	5.773	63.244	85.515	1.00	22.58
ATOM	317	O	TYR	A	49	5.797	62.383	86.390	1.00	24.04
ATOM	318	CB	TYR	A	49	7.304	65.282	85.217	1.00	20.61
ATOM	319	CG	TYR	A	49	7.034	65.494	86.692	1.00	23.57
ATOM	320	CD1	TYR	A	49	5.755	65.931	87.109	1.00	23.57
ATOM	321	CD2	TYR	A	49	8.080	65.194	87.574	1.00	21.83
ATOM	322	CE1	TYR	A	49	5.524	66.097	88.481	1.00	26.09
ATOM	323	CE2	TYR	A	49	7.844	65.349	88.943	1.00	23.18
ATOM	324	CZ	TYR	A	49	6.591	65.842	89.377	1.00	26.31



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ATOM	325	OH	TYR	A	49	6.444	66.124	90.726	1.00	29.46
ATOM	326	N	GLU	A	50	4.639	63.731	84.994	1.00	22.09
ATOM	327	CA	GLU	A	50	3.336	63.234	85.472	1.00	21.48
ATOM	328	C	GLU	A	50	3.052	61.776	85.230	1.00	23.20
ATOM	329	O	GLU	A	50	2.548	61.050	86.081	1.00	24.23
ATOM	330	CB	GLU	A	50	2.190	64.023	84.862	1.00	21.88
ATOM	331	CG	GLU	A	50	2.304	65.537	84.986	1.00	21.13
ATOM	332	CD	GLU	A	50	2.054	65.976	86.417	1.00	25.41
ATOM	333	OE1	GLU	A	50	1.887	65.138	87.287	1.00	24.65
ATOM	334	OE2	GLU	A	50	2.004	67.162	86.679	1.00	25.05
ATOM	335	N	GLN	A	51	3.479	61.343	84.032	1.00	23.02
ATOM	336	CA	GLN	A	51	3.427	59.907	83.812	1.00	24.72
ATOM	337	C	GLN	A	51	4.275	59.006	84.728	1.00	26.23
ATOM	338	O	GLN	A	51	3.804	57.996	85.253	1.00	25.10
ATOM	339	CB	GLN	A	51	3.680	59.545	82.355	1.00	24.41
ATOM	340	CG	GLN	A	51	3.461	58.028	82.141	1.00	38.05
ATOM	341	CD	GLN	A	51	2.115	57.435	82.657	1.00	53.15
ATOM	342	OE1	GLN	A	51	1.093	58.076	82.867	1.00	61.03
ATOM	343	NE2	GLN	A	51	2.098	56.123	82.834	1.00	55.24
ATOM	344	N	GLY	A	52	5.556	59.414	84.922	1.00	26.76
ATOM	345	CA	GLY	A	52	6.400	58.689	85.876	1.00	26.91
ATOM	346	C	GLY	A	52	5.793	58.681	87.286	1.00	25.60
ATOM	347	O	GLY	A	52	5.666	57.699	87.997	1.00	24.37
ATOM	348	N	ARG	A	53	5.321	59.874	87.621	1.00	28.09
ATOM	349	CA	ARG	A	53	4.527	60.032	88.834	1.00	29.75
ATOM	350	C	ARG	A	53	3.384	59.049	89.067	1.00	32.01
ATOM	351	O	ARG	A	53	3.284	58.437	90.115	1.00	34.69
ATOM	352	CB	ARG	A	53	4.128	61.494	88.965	1.00	30.41
ATOM	353	CG	ARG	A	53	3.857	61.919	90.389	1.00	29.15
ATOM	354	CD	ARG	A	53	3.519	63.393	90.461	1.00	29.38
ATOM	355	NE	ARG	A	53	2.385	63.740	89.609	1.00	31.35
ATOM	356	CZ	ARG	A	53	1.088	63.593	89.886	1.00	32.29
ATOM	357	NH1	ARG	A	53	0.187	64.144	89.125	1.00	32.06
ATOM	358	NH2	ARG	A	53	0.661	62.938	90.931	1.00	32.66
ATOM	359	N	LEU	A	54	2.575	58.839	88.033	1.00	32.47
ATOM	360	CA	LEU	A	54	1.588	57.735	88.076	1.00	31.67
ATOM	361	C	LEU	A	54	2.114	56.273	88.119	1.00	33.30
ATOM	362	O	LEU	A	54	1.452	55.329	88.568	1.00	35.90
ATOM	363	CB	LEU	A	54	0.603	57.880	86.901	1.00	33.52
ATOM	364	CG	LEU	A	54	-0.599	58.822	87.055	1.00	32.85
ATOM	365	CD1	LEU	A	54	-1.298	59.020	85.709	1.00	30.53
ATOM	366	CD2	LEU	A	54	-0.286	60.130	87.777	1.00	36.56
ATOM	367	N	LEU	A	55	3.374	56.117	87.657	1.00	31.95
ATOM	368	CA	LEU	A	55	4.016	54.784	87.735	1.00	32.70
ATOM	369	C	LEU	A	55	4.577	54.392	89.091	1.00	33.98
ATOM	370	O	LEU	A	55	4.842	53.224	89.386	1.00	32.73
ATOM	371	CB	LEU	A	55	5.194	54.646	86.790	1.00	31.04
ATOM	372	CG	LEU	A	55	4.832	54.514	85.343	1.00	28.60
ATOM	373	CD1	LEU	A	55	3.960	53.287	85.101	1.00	27.88
ATOM	374	CD2	LEU	A	55	6.118	54.471	84.539	1.00	28.33
ATOM	375	N	ARG	A	56	4.732	55.458	89.911	1.00	36.20
ATOM	376	CA	ARG	A	56	5.257	55.308	91.281	1.00	37.04
ATOM	377	C	ARG	A	56	4.616	54.240	92.164	1.00	40.28
ATOM	378	O	ARG	A	56	5.260	53.518	92.907	1.00	41.22

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ATOM	379	CB	ARG	A	56	5.249	56.643	91.993	1.00	32.58
ATOM	380	CG	ARG	A	56	6.368	57.502	91.476	1.00	22.04
ATOM	381	CD	ARG	A	56	6.142	58.874	92.049	1.00	21.74
ATOM	382	NE	ARG	A	56	7.073	59.804	91.447	1.00	23.56
ATOM	383	CZ	ARG	A	56	7.062	61.074	91.750	1.00	25.56
ATOM	384	NH1	ARG	A	56	6.401	61.444	92.790	1.00	30.94
ATOM	385	NH2	ARG	A	56	7.688	61.979	91.035	1.00	22.33
ATOM	386	N	ASN	A	57	3.306	54.120	91.997	1.00	44.42
ATOM	387	CA	ASN	A	57	2.602	53.027	92.680	1.00	48.62
ATOM	388	C	ASN	A	57	2.786	51.585	92.169	1.00	47.46
ATOM	389	O	ASN	A	57	2.316	50.630	92.759	1.00	51.15
ATOM	390	CB	ASN	A	57	1.124	53.435	92.726	1.00	59.30
ATOM	391	CG	ASN	A	57	0.389	53.137	94.049	1.00	68.98
ATOM	392	OD1	ASN	A	57	-0.829	53.335	94.164	1.00	75.09
ATOM	393	ND2	ASN	A	57	1.140	52.692	95.058	1.00	71.68
ATOM	394	N	THR	A	58	3.461	51.442	91.036	1.00	42.68
ATOM	395	CA	THR	A	58	3.555	50.086	90.475	1.00	36.64
ATOM	396	C	THR	A	58	4.821	49.318	90.871	1.00	33.64
ATOM	397	O	THR	A	58	5.721	49.876	91.477	1.00	31.69
ATOM	398	CB	THR	A	58	3.492	50.189	88.948	1.00	36.81
ATOM	399	OG1	THR	A	58	4.774	50.576	88.447	1.00	37.64
ATOM	400	CG2	THR	A	58	2.432	51.203	88.507	1.00	35.36
ATOM	401	N	GLU	A	59	4.937	48.068	90.409	1.00	33.08
ATOM	402	CA	GLU	A	59	6.238	47.410	90.581	1.00	34.80
ATOM	403	C	GLU	A	59	7.487	48.104	89.944	1.00	33.45
ATOM	404	O	GLU	A	59	8.607	48.153	90.463	1.00	34.28
ATOM	405	CB	GLU	A	59	6.067	45.933	90.191	1.00	43.43
ATOM	406	CG	GLU	A	59	7.242	45.007	90.614	1.00	59.74
ATOM	407	CD	GLU	A	59	7.519	44.933	92.159	1.00	69.61
ATOM	408	OE1	GLU	A	59	6.582	45.064	92.960	1.00	74.78
ATOM	409	OE2	GLU	A	59	8.686	44.751	92.589	1.00	74.97
ATOM	410	N	ARG	A	60	7.229	48.734	88.768	1.00	27.61
ATOM	411	CA	ARG	A	60	8.251	49.599	88.158	1.00	25.02
ATOM	412	C	ARG	A	60	8.614	50.851	88.958	1.00	22.94
ATOM	413	O	ARG	A	60	9.772	51.257	89.002	1.00	24.63
ATOM	414	CB	ARG	A	60	7.874	49.966	86.690	1.00	26.16
ATOM	415	CG	ARG	A	60	8.877	50.860	85.900	1.00	24.47
ATOM	416	CD	ARG	A	60	10.268	50.249	85.758	1.00	23.96
ATOM	417	NE	ARG	A	60	11.285	51.161	85.217	1.00	25.64
ATOM	418	CZ	ARG	A	60	12.214	51.778	85.945	1.00	24.77
ATOM	419	NH1	ARG	A	60	12.159	51.805	87.261	1.00	24.78
ATOM	420	NH2	ARG	A	60	13.227	52.294	85.325	1.00	19.79
ATOM	421	N	GLY	A	61	7.562	51.411	89.587	1.00	21.94
ATOM	422	CA	GLY	A	61	7.623	52.443	90.620	1.00	22.33
ATOM	423	C	GLY	A	61	8.468	52.051	91.824	1.00	24.44
ATOM	424	O	GLY	A	61	9.350	52.773	92.253	1.00	25.22
ATOM	425	N	LYS	A	62	8.248	50.821	92.307	1.00	26.95
ATOM	426	CA	LYS	A	62	9.102	50.251	93.350	1.00	26.24
ATOM	427	C	LYS	A	62	10.590	50.158	93.045	1.00	24.89
ATOM	428	O	LYS	A	62	11.443	50.668	93.756	1.00	23.23
ATOM	429	CB	LYS	A	62	8.519	48.900	93.723	1.00	29.90
ATOM	430	CG	LYS	A	62	9.379	48.296	94.835	1.00	38.76
ATOM	431	CD	LYS	A	62	8.847	46.904	95.222	1.00	47.47
ATOM	432	CE	LYS	A	62	9.944	45.971	95.773	1.00	53.72

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ATOM	433	NZ	LYS	A	62	10.167	44.857	94.832	1.00	60.22
ATOM	434	N	LEU	A	63	10.866	49.560	91.882	1.00	24.67
ATOM	435	CA	LEU	A	63	12.239	49.634	91.346	1.00	23.65
ATOM	436	C	LEU	A	63	12.805	51.043	91.186	1.00	22.74
ATOM	437	O	LEU	A	63	13.927	51.359	91.517	1.00	25.19
ATOM	438	CB	LEU	A	63	12.232	48.973	89.981	1.00	27.11
ATOM	439	CG	LEU	A	63	13.477	48.298	89.403	1.00	31.83
ATOM	440	CD1	LEU	A	63	14.808	48.658	90.077	1.00	33.84
ATOM	441	CD2	LEU	A	63	13.440	48.410	87.874	1.00	26.95
ATOM	442	N	ALA	A	64	11.979	51.940	90.642	1.00	21.62
ATOM	443	CA	ALA	A	64	12.492	53.308	90.539	1.00	20.51
ATOM	444	C	ALA	A	64	12.862	53.971	91.863	1.00	21.79
ATOM	445	O	ALA	A	64	13.890	54.636	91.984	1.00	21.21
ATOM	446	CB	ALA	A	64	11.456	54.196	89.862	1.00	19.01
ATOM	447	N	ALA	A	65	11.984	53.747	92.870	1.00	23.25
ATOM	448	CA	ALA	A	65	12.374	54.212	94.235	1.00	24.88
ATOM	449	C	ALA	A	65	13.684	53.619	94.784	1.00	22.62
ATOM	450	O	ALA	A	65	14.551	54.328	95.268	1.00	22.95
ATOM	451	CB	ALA	A	65	11.249	54.013	95.265	1.00	25.38
ATOM	452	N	GLU	A	66	13.848	52.295	94.572	1.00	23.38
ATOM	453	CA	GLU	A	66	15.116	51.632	94.878	1.00	23.41
ATOM	454	C	GLU	A	66	16.332	52.188	94.152	1.00	26.06
ATOM	455	O	GLU	A	66	17.321	52.604	94.744	1.00	25.12
ATOM	456	CB	GLU	A	66	14.968	50.136	94.665	1.00	25.85
ATOM	457	CG	GLU	A	66	13.818	49.616	95.533	1.00	31.94
ATOM	458	CD	GLU	A	66	13.546	48.142	95.293	1.00	37.59
ATOM	459	OE1	GLU	A	66	13.147	47.430	96.220	1.00	40.33
ATOM	460	OE2	GLU	A	66	13.721	47.673	94.176	1.00	40.79
ATOM	461	N	ASP	A	67	16.204	52.276	92.817	1.00	24.01
ATOM	462	CA	ASP	A	67	17.222	52.928	91.986	1.00	19.72
ATOM	463	C	ASP	A	67	17.549	54.333	92.402	1.00	16.72
ATOM	464	O	ASP	A	67	18.694	54.767	92.414	1.00	18.91
ATOM	465	CB	ASP	A	67	16.787	52.944	90.495	1.00	21.68
ATOM	466	CG	ASP	A	67	16.824	51.580	89.801	1.00	25.22
ATOM	467	OD1	ASP	A	67	17.340	50.629	90.370	1.00	23.32
ATOM	468	OD2	ASP	A	67	16.349	51.434	88.666	1.00	26.83
ATOM	469	N	ALA	A	68	16.485	55.059	92.773	1.00	16.48
ATOM	470	CA	ALA	A	68	16.685	56.425	93.250	1.00	19.28
ATOM	471	C	ALA	A	68	17.489	56.510	94.569	1.00	20.86
ATOM	472	O	ALA	A	68	18.165	57.494	94.837	1.00	22.07
ATOM	473	CB	ALA	A	68	15.330	57.134	93.419	1.00	19.81
ATOM	474	N	ASN	A	69	17.472	55.371	95.299	1.00	23.11
ATOM	475	CA	ASN	A	69	18.330	55.262	96.514	1.00	27.41
ATOM	476	C	ASN	A	69	19.816	55.042	96.273	1.00	29.49
ATOM	477	O	ASN	A	69	20.646	55.304	97.140	1.00	28.64
ATOM	478	CB	ASN	A	69	17.933	54.145	97.466	1.00	24.19
ATOM	479	CG	ASN	A	69	16.632	54.425	98.142	1.00	25.79
ATOM	480	OD1	ASN	A	69	16.298	55.549	98.445	1.00	26.84
ATOM	481	ND2	ASN	A	69	15.894	53.359	98.410	1.00	30.16
ATOM	482	N	LEU	A	70	20.104	54.574	95.034	1.00	25.30
ATOM	483	CA	LEU	A	70	21.514	54.442	94.627	1.00	23.20
ATOM	484	C	LEU	A	70	22.329	55.691	94.640	1.00	21.41
ATOM	485	O	LEU	A	70	22.013	56.696	94.028	1.00	23.50
ATOM	486	CB	LEU	A	70	21.672	53.890	93.225	1.00	22.19

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ATOM	487	CG	LEU	A	70	21.078	52.512	93.095	1.00	22.16
ATOM	488	CD1	LEU	A	70	21.830	51.459	93.896	1.00	20.70
ATOM	489	CD2	LEU	A	70	21.016	52.154	91.624	1.00	23.47
ATOM	490	N	SER	A	71	23.450	55.563	95.304	1.00	21.73
ATOM	491	CA	SER	A	71	24.527	56.515	95.119	1.00	22.25
ATOM	492	C	SER	A	71	25.355	56.171	93.888	1.00	20.52
ATOM	493	O	SER	A	71	25.269	55.081	93.357	1.00	23.70
ATOM	494	CB	SER	A	71	25.453	56.521	96.349	1.00	22.74
ATOM	495	OG	SER	A	71	26.232	55.303	96.432	1.00	28.68
ATOM	496	N	SER	A	72	26.220	57.079	93.445	1.00	20.02
ATOM	497	CA	SER	A	72	27.096	56.747	92.294	1.00	20.88
ATOM	498	C	SER	A	72	27.860	55.479	92.410	1.00	22.52
ATOM	499	O	SER	A	72	27.979	54.663	91.518	1.00	21.65
ATOM	500	CB	SER	A	72	28.113	57.834	92.083	1.00	19.05
ATOM	501	OG	SER	A	72	27.352	58.966	91.735	1.00	22.00
ATOM	502	N	GLY	A	73	28.336	55.318	93.640	1.00	20.71
ATOM	503	CA	GLY	A	73	28.979	54.068	94.006	1.00	16.81
ATOM	504	C	GLY	A	73	28.146	52.783	93.939	1.00	15.97
ATOM	505	O	GLY	A	73	28.697	51.705	93.753	1.00	20.02
ATOM	506	N	GLY	A	74	26.818	52.915	94.046	1.00	16.07
ATOM	507	CA	GLY	A	74	26.090	51.649	93.967	1.00	18.17
ATOM	508	C	GLY	A	74	25.671	51.260	92.526	1.00	21.98
ATOM	509	O	GLY	A	74	25.202	50.164	92.238	1.00	21.28
ATOM	510	N	VAL	A	75	25.887	52.210	91.567	1.00	22.48
ATOM	511	CA	VAL	A	75	25.521	51.777	90.174	1.00	22.71
ATOM	512	C	VAL	A	75	26.174	50.493	89.628	1.00	18.50
ATOM	513	O	VAL	A	75	25.497	49.573	89.210	1.00	20.32
ATOM	514	CB	VAL	A	75	25.820	52.946	89.218	1.00	23.52
ATOM	515	CG1	VAL	A	75	25.719	52.707	87.712	1.00	21.49
ATOM	516	CG2	VAL	A	75	25.153	54.265	89.560	1.00	17.54
ATOM	517	N	ALA	A	76	27.517	50.394	89.738	1.00	21.05
ATOM	518	CA	ALA	A	76	28.149	49.125	89.372	1.00	20.51
ATOM	519	C	ALA	A	76	27.414	47.875	89.826	1.00	24.64
ATOM	520	O	ALA	A	76	27.033	47.028	89.015	1.00	24.90
ATOM	521	CB	ALA	A	76	29.612	49.071	89.810	1.00	19.14
ATOM	522	N	ASN	A	77	27.131	47.820	91.145	1.00	20.97
ATOM	523	CA	ASN	A	77	26.463	46.601	91.622	1.00	17.62
ATOM	524	C	ASN	A	77	25.019	46.464	91.205	1.00	16.57
ATOM	525	O	ASN	A	77	24.536	45.350	91.024	1.00	19.24
ATOM	526	CB	ASN	A	77	26.615	46.509	93.137	1.00	23.52
ATOM	527	CG	ASN	A	77	25.817	45.362	93.677	1.00	21.57
ATOM	528	OD1	ASN	A	77	24.672	45.508	94.079	1.00	26.66
ATOM	529	ND2	ASN	A	77	26.435	44.202	93.627	1.00	24.64
ATOM	530	N	ALA	A	78	24.377	47.638	91.017	1.00	17.23
ATOM	531	CA	ALA	A	78	23.060	47.710	90.339	1.00	18.62
ATOM	532	C	ALA	A	78	22.874	47.025	88.941	1.00	19.92
ATOM	533	O	ALA	A	78	21.767	46.705	88.517	1.00	21.04
ATOM	534	CB	ALA	A	78	22.636	49.160	90.208	1.00	13.62
ATOM	535	N	PHE	A	79	24.025	46.748	88.292	1.00	19.22
ATOM	536	CA	PHE	A	79	24.019	45.921	87.070	1.00	20.71
ATOM	537	C	PHE	A	79	24.117	44.420	87.238	1.00	23.30
ATOM	538	O	PHE	A	79	24.161	43.662	86.273	1.00	23.64
ATOM	539	CB	PHE	A	79	25.116	46.352	86.082	1.00	18.00
ATOM	540	CG	PHE	A	79	24.821	47.683	85.382	1.00	19.59

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ATOM	541	CD1	PHE	A	79	25.181	48.903	85.984	1.00	17.05
ATOM	542	CD2	PHE	A	79	24.214	47.687	84.104	1.00	18.56
ATOM	543	CE1	PHE	A	79	25.026	50.119	85.298	1.00	19.06
ATOM	544	CE2	PHE	A	79	24.040	48.906	83.419	1.00	15.97
ATOM	545	CZ	PHE	A	79	24.500	50.104	83.989	1.00	17.87
ATOM	546	N	SER	A	80	24.150	43.947	88.488	1.00	19.74
ATOM	547	CA	SER	A	80	24.500	42.511	88.632	1.00	17.29
ATOM	548	C	SER	A	80	23.601	41.501	87.944	1.00	18.57
ATOM	549	O	SER	A	80	23.977	40.494	87.339	1.00	22.38
ATOM	550	CB	SER	A	80	24.608	42.106	90.125	1.00	15.17
ATOM	551	OG	SER	A	80	25.646	42.920	90.700	1.00	17.32
ATOM	552	N	GLY	A	81	22.309	41.852	88.041	1.00	19.68
ATOM	553	CA	GLY	A	81	21.271	41.005	87.413	1.00	22.50
ATOM	554	C	GLY	A	81	21.293	40.977	85.855	1.00	24.85
ATOM	555	O	GLY	A	81	21.318	39.939	85.211	1.00	23.46
ATOM	556	N	ALA	A	82	21.380	42.197	85.279	1.00	24.60
ATOM	557	CA	ALA	A	82	21.686	42.339	83.855	1.00	24.50
ATOM	558	C	ALA	A	82	22.985	41.643	83.417	1.00	25.22
ATOM	559	O	ALA	A	82	23.000	40.873	82.468	1.00	23.42
ATOM	560	CB	ALA	A	82	21.649	43.819	83.470	1.00	20.35
ATOM	561	N	PHE	A	83	24.050	41.874	84.197	1.00	23.76
ATOM	562	CA	PHE	A	83	25.319	41.242	83.894	1.00	21.76
ATOM	563	C	PHE	A	83	25.325	39.726	83.974	1.00	22.85
ATOM	564	O	PHE	A	83	26.090	39.052	83.322	1.00	25.72
ATOM	565	CB	PHE	A	83	26.349	41.867	84.792	1.00	20.01
ATOM	566	CG	PHE	A	83	27.770	41.527	84.394	1.00	20.95
ATOM	567	CD1	PHE	A	83	28.486	40.587	85.152	1.00	16.94
ATOM	568	CD2	PHE	A	83	28.391	42.208	83.307	1.00	23.09
ATOM	569	CE1	PHE	A	83	29.841	40.355	84.843	1.00	18.79
ATOM	570	CE2	PHE	A	83	29.751	41.991	83.001	1.00	20.95
ATOM	571	CZ	PHE	A	83	30.474	41.069	83.795	1.00	21.43
ATOM	572	N	GLY	A	84	24.409	39.187	84.768	1.00	22.31
ATOM	573	CA	GLY	A	84	24.478	37.740	84.865	1.00	24.39
ATOM	574	C	GLY	A	84	25.199	37.163	86.093	1.00	29.49
ATOM	575	O	GLY	A	84	25.158	35.963	86.362	1.00	32.27
ATOM	576	N	SER	A	85	25.873	38.058	86.843	1.00	30.33
ATOM	577	CA	SER	A	85	26.685	37.625	88.001	1.00	28.46
ATOM	578	C	SER	A	85	27.047	38.788	88.936	1.00	29.06
ATOM	579	O	SER	A	85	26.915	39.945	88.556	1.00	29.00
ATOM	580	CB	SER	A	85	27.915	36.861	87.536	1.00	24.04
ATOM	581	OG	SER	A	85	28.903	37.746	87.028	1.00	28.11
ATOM	582	N	PRO	A	86	27.436	38.518	90.216	1.00	29.45
ATOM	583	CA	PRO	A	86	27.599	39.650	91.122	1.00	26.27
ATOM	584	C	PRO	A	86	28.721	40.513	90.733	1.00	22.75
ATOM	585	O	PRO	A	86	29.830	40.064	90.530	1.00	22.43
ATOM	586	CB	PRO	A	86	27.873	39.029	92.493	1.00	27.52
ATOM	587	CG	PRO	A	86	27.284	37.627	92.399	1.00	27.61
ATOM	588	CD	PRO	A	86	27.591	37.258	90.945	1.00	31.08
ATOM	589	N	ILE	A	87	28.350	41.776	90.659	1.00	22.99
ATOM	590	CA	ILE	A	87	29.363	42.816	90.469	1.00	24.80
ATOM	591	C	ILE	A	87	29.642	43.494	91.811	1.00	25.76
ATOM	592	O	ILE	A	87	28.956	44.424	92.220	1.00	24.68
ATOM	593	CB	ILE	A	87	28.908	43.860	89.427	1.00	24.26
ATOM	594	CG1	ILE	A	87	28.626	43.165	88.076	1.00	23.29

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ATOM	595	CG2	ILE	A	87	29.997	44.923	89.306	1.00	23.62
ATOM	596	CD1	ILE	A	87	27.925	44.100	87.092	1.00	21.95
ATOM	597	N	THR	A	88	30.655	42.914	92.481	1.00	25.86
ATOM	598	CA	THR	A	88	30.925	43.247	93.903	1.00	25.48
ATOM	599	C	THR	A	88	32.418	43.249	94.166	1.00	25.25
ATOM	600	O	THR	A	88	33.131	42.561	93.445	1.00	24.26
ATOM	601	CB	THR	A	88	30.332	42.211	94.859	1.00	22.31
ATOM	602	OG1	THR	A	88	31.102	41.029	94.702	1.00	25.42
ATOM	603	CG2	THR	A	88	28.833	41.943	94.710	1.00	19.45
ATOM	604	N	GLU	A	89	32.891	43.970	95.204	1.00	26.63
ATOM	605	CA	GLU	A	89	34.322	43.845	95.577	1.00	25.29
ATOM	606	C	GLU	A	89	34.810	42.429	95.889	1.00	25.30
ATOM	607	O	GLU	A	89	35.924	41.999	95.611	1.00	26.30
ATOM	608	CB	GLU	A	89	34.652	44.773	96.741	1.00	25.64
ATOM	609	CG	GLU	A	89	34.334	46.193	96.340	1.00	26.52
ATOM	610	CD	GLU	A	89	34.551	47.228	97.414	1.00	29.70
ATOM	611	OE1	GLU	A	89	35.136	48.245	97.123	1.00	33.05
ATOM	612	OE2	GLU	A	89	34.138	47.077	98.540	1.00	27.59
ATOM	613	N	LYS	A	90	33.860	41.697	96.459	1.00	26.25
ATOM	614	CA	LYS	A	90	34.095	40.310	96.883	1.00	28.81
ATOM	615	C	LYS	A	90	34.285	39.313	95.780	1.00	28.19
ATOM	616	O	LYS	A	90	35.206	38.518	95.773	1.00	30.49
ATOM	617	CB	LYS	A	90	32.889	39.869	97.672	1.00	31.00
ATOM	618	CG	LYS	A	90	32.956	38.478	98.228	1.00	37.00
ATOM	619	CD	LYS	A	90	31.536	38.026	98.583	1.00	43.53
ATOM	620	CE	LYS	A	90	31.386	36.504	98.712	1.00	50.17
ATOM	621	NZ	LYS	A	90	32.257	35.875	97.701	1.00	60.80
ATOM	622	N	ASP	A	91	33.324	39.416	94.870	1.00	28.68
ATOM	623	CA	ASP	A	91	33.271	38.504	93.738	1.00	29.34
ATOM	624	C	ASP	A	91	33.911	38.947	92.420	1.00	29.37
ATOM	625	O	ASP	A	91	34.429	38.173	91.635	1.00	31.54
ATOM	626	CB	ASP	A	91	31.827	38.162	93.438	1.00	30.91
ATOM	627	CG	ASP	A	91	31.087	37.722	94.674	1.00	31.69
ATOM	628	OD1	ASP	A	91	31.395	36.657	95.212	1.00	35.66
ATOM	629	OD2	ASP	A	91	30.186	38.438	95.088	1.00	29.63
ATOM	630	N	ALA	A	92	33.830	40.240	92.165	1.00	28.62
ATOM	631	CA	ALA	A	92	34.443	40.713	90.919	1.00	26.75
ATOM	632	C	ALA	A	92	35.255	41.981	91.131	1.00	26.94
ATOM	633	O	ALA	A	92	34.937	43.081	90.690	1.00	26.94
ATOM	634	CB	ALA	A	92	33.390	40.934	89.817	1.00	23.93
ATOM	635	N	PRO	A	93	36.336	41.826	91.930	1.00	27.16
ATOM	636	CA	PRO	A	93	37.151	43.015	92.274	1.00	25.78
ATOM	637	C	PRO	A	93	37.832	43.865	91.160	1.00	24.62
ATOM	638	O	PRO	A	93	37.844	45.098	91.178	1.00	22.75
ATOM	639	CB	PRO	A	93	38.120	42.411	93.292	1.00	25.31
ATOM	640	CG	PRO	A	93	38.219	40.926	92.945	1.00	23.54
ATOM	641	CD	PRO	A	93	36.817	40.578	92.534	1.00	25.29
ATOM	642	N	ALA	A	94	38.409	43.174	90.170	1.00	25.16
ATOM	643	CA	ALA	A	94	38.954	43.886	89.005	1.00	23.77
ATOM	644	C	ALA	A	94	37.923	44.715	88.249	1.00	17.72
ATOM	645	O	ALA	A	94	38.116	45.897	88.005	1.00	19.91
ATOM	646	CB	ALA	A	94	39.676	42.931	88.058	1.00	21.52
ATOM	647	N	LEU	A	95	36.787	44.081	88.026	1.00	19.68
ATOM	648	CA	LEU	A	95	35.577	44.770	87.539	1.00	20.23

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ATOM	649	C	LEU	A	95	35.001	45.902	88.385	1.00	21.85
ATOM	650	O	LEU	A	95	34.809	47.026	87.943	1.00	21.66
ATOM	651	CB	LEU	A	95	34.466	43.755	87.271	1.00	20.70
ATOM	652	CG	LEU	A	95	33.250	44.285	86.467	1.00	21.32
ATOM	653	CD1	LEU	A	95	32.299	43.149	86.063	1.00	20.10
ATOM	654	CD2	LEU	A	95	33.698	45.111	85.240	1.00	20.93
ATOM	655	N	HIS	A	96	34.755	45.606	89.667	1.00	21.70
ATOM	656	CA	HIS	A	96	34.313	46.691	90.543	1.00	17.84
ATOM	657	C	HIS	A	96	35.214	47.924	90.580	1.00	17.76
ATOM	658	O	HIS	A	96	34.767	49.069	90.496	1.00	19.44
ATOM	659	CB	HIS	A	96	34.042	46.116	91.937	1.00	20.62
ATOM	660	CG	HIS	A	96	32.934	46.893	92.613	1.00	21.96
ATOM	661	ND1	HIS	A	96	33.021	48.094	93.229	1.00	21.34
ATOM	662	CD2	HIS	A	96	31.614	46.470	92.680	1.00	24.62
ATOM	663	CE1	HIS	A	96	31.790	48.442	93.690	1.00	18.16
ATOM	664	NE2	HIS	A	96	30.923	47.437	93.338	1.00	23.59
ATOM	665	N	LYS	A	97	36.539	47.639	90.629	1.00	18.11
ATOM	666	CA	LYS	A	97	37.544	48.713	90.581	1.00	18.50
ATOM	667	C	LYS	A	97	37.519	49.564	89.317	1.00	20.80
ATOM	668	O	LYS	A	97	37.452	50.781	89.373	1.00	21.08
ATOM	669	CB	LYS	A	97	38.924	48.085	90.766	1.00	17.26
ATOM	670	CG	LYS	A	97	40.125	49.014	90.594	1.00	21.24
ATOM	671	CD	LYS	A	97	40.283	50.213	91.525	1.00	30.10
ATOM	672	CE	LYS	A	97	41.482	51.160	91.164	1.00	33.55
ATOM	673	NZ	LYS	A	97	41.557	52.449	91.915	1.00	29.55
ATOM	674	N	LEU	A	98	37.532	48.857	88.155	1.00	22.36
ATOM	675	CA	LEU	A	98	37.291	49.555	86.851	1.00	22.04
ATOM	676	C	LEU	A	98	36.128	50.581	86.806	1.00	17.59
ATOM	677	O	LEU	A	98	36.223	51.763	86.522	1.00	18.13
ATOM	678	CB	LEU	A	98	37.025	48.477	85.780	1.00	21.44
ATOM	679	CG	LEU	A	98	36.766	49.042	84.375	1.00	20.93
ATOM	680	CD1	LEU	A	98	36.265	47.902	83.493	1.00	22.92
ATOM	681	CD2	LEU	A	98	37.963	49.801	83.811	1.00	18.27
ATOM	682	N	LEU	A	99	34.977	50.024	87.188	1.00	19.16
ATOM	683	CA	LEU	A	99	33.753	50.802	87.186	1.00	18.37
ATOM	684	C	LEU	A	99	33.644	51.930	88.169	1.00	20.61
ATOM	685	O	LEU	A	99	33.068	52.964	87.883	1.00	18.31
ATOM	686	CB	LEU	A	99	32.545	49.874	87.263	1.00	18.90
ATOM	687	CG	LEU	A	99	32.428	48.860	86.191	1.00	20.87
ATOM	688	CD1	LEU	A	99	32.464	49.503	84.841	1.00	14.73
ATOM	689	CD2	LEU	A	99	31.190	48.099	86.497	1.00	19.82
ATOM	690	N	THR	A	100	34.252	51.692	89.359	1.00	22.03
ATOM	691	CA	THR	A	100	34.357	52.777	90.360	1.00	19.41
ATOM	692	C	THR	A	100	35.259	53.938	89.957	1.00	16.72
ATOM	693	O	THR	A	100	34.984	55.118	90.136	1.00	16.55
ATOM	694	CB	THR	A	100	34.889	52.174	91.674	1.00	19.50
ATOM	695	OG1	THR	A	100	34.030	51.113	92.091	1.00	19.99
ATOM	696	CG2	THR	A	100	35.092	53.221	92.758	1.00	21.12
ATOM	697	N	ASN	A	101	36.397	53.537	89.358	1.00	20.56
ATOM	698	CA	ASN	A	101	37.415	54.515	88.998	1.00	19.91
ATOM	699	C	ASN	A	101	37.022	55.479	87.873	1.00	21.88
ATOM	700	O	ASN	A	101	37.610	56.546	87.711	1.00	22.38
ATOM	701	CB	ASN	A	101	38.692	53.763	88.716	1.00	20.98
ATOM	702	CG	ASN	A	101	39.950	54.556	89.041	1.00	22.36

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ATOM	703	OD1	ASN	A	101	40.938	53.978	89.459	1.00	30.43
ATOM	704	ND2	ASN	A	101	39.964	55.868	88.889	1.00	23.45
ATOM	705	N	MET	A	102	35.952	55.090	87.154	1.00	21.94
ATOM	706	CA	MET	A	102	35.407	55.984	86.103	1.00	22.28
ATOM	707	C	MET	A	102	34.142	56.755	86.455	1.00	22.36
ATOM	708	O	MET	A	102	33.571	57.482	85.638	1.00	23.37
ATOM	709	CB	MET	A	102	35.162	55.213	84.781	1.00	19.03
ATOM	710	CG	MET	A	102	34.239	54.001	84.972	1.00	18.05
ATOM	711	SD	MET	A	102	33.744	53.082	83.481	1.00	20.07
ATOM	712	CE	MET	A	102	32.429	54.165	83.010	1.00	16.04
ATOM	713	N	ILE	A	103	33.681	56.555	87.724	1.00	21.00
ATOM	714	CA	ILE	A	103	32.441	57.221	88.180	1.00	18.78
ATOM	715	C	ILE	A	103	32.371	58.697	87.833	1.00	17.38
ATOM	716	O	ILE	A	103	31.413	59.152	87.245	1.00	18.08
ATOM	717	CB	ILE	A	103	32.174	57.025	89.732	1.00	16.18
ATOM	718	CG1	ILE	A	103	31.696	55.603	90.031	1.00	19.21
ATOM	719	CG2	ILE	A	103	31.135	58.037	90.272	1.00	12.63
ATOM	720	CD1	ILE	A	103	31.708	55.185	91.522	1.00	17.58
ATOM	721	N	GLU	A	104	33.426	59.429	88.218	1.00	18.81
ATOM	722	CA	GLU	A	104	33.369	60.900	88.092	1.00	18.36
ATOM	723	C	GLU	A	104	33.828	61.520	86.772	1.00	19.60
ATOM	724	O	GLU	A	104	33.420	62.606	86.365	1.00	19.13
ATOM	725	CB	GLU	A	104	34.092	61.600	89.241	1.00	18.56
ATOM	726	CG	GLU	A	104	33.446	61.448	90.617	1.00	19.21
ATOM	727	CD	GLU	A	104	31.994	61.944	90.665	1.00	23.36
ATOM	728	OE1	GLU	A	104	31.225	61.359	91.382	1.00	26.94
ATOM	729	OE2	GLU	A	104	31.574	62.888	90.013	1.00	28.46
ATOM	730	N	ASP	A	105	34.606	60.713	86.049	1.00	18.95
ATOM	731	CA	ASP	A	105	34.743	60.936	84.587	1.00	17.40
ATOM	732	C	ASP	A	105	33.378	61.099	83.886	1.00	15.12
ATOM	733	O	ASP	A	105	33.104	62.102	83.234	1.00	18.61
ATOM	734	CB	ASP	A	105	35.429	59.743	83.951	1.00	16.81
ATOM	735	CG	ASP	A	105	36.831	59.545	84.440	1.00	15.10
ATOM	736	OD1	ASP	A	105	37.573	60.520	84.573	1.00	19.01
ATOM	737	OD2	ASP	A	105	37.177	58.402	84.685	1.00	15.56
ATOM	738	N	ALA	A	106	32.500	60.091	84.096	1.00	15.05
ATOM	739	CA	ALA	A	106	31.111	60.157	83.607	1.00	15.61
ATOM	740	C	ALA	A	106	30.166	61.126	84.315	1.00	19.62
ATOM	741	O	ALA	A	106	29.409	61.881	83.720	1.00	18.83
ATOM	742	CB	ALA	A	106	30.467	58.782	83.682	1.00	11.73
ATOM	743	N	GLY	A	107	30.263	61.102	85.674	1.00	21.49
ATOM	744	CA	GLY	A	107	29.323	61.899	86.503	1.00	16.83
ATOM	745	C	GLY	A	107	29.599	63.356	86.594	1.00	14.80
ATOM	746	O	GLY	A	107	28.714	64.204	86.575	1.00	17.67
ATOM	747	N	ASP	A	108	30.899	63.611	86.662	1.00	16.37
ATOM	748	CA	ASP	A	108	31.305	65.002	86.772	1.00	17.18
ATOM	749	C	ASP	A	108	31.877	65.572	85.485	1.00	18.56
ATOM	750	O	ASP	A	108	31.324	66.472	84.877	1.00	18.77
ATOM	751	CB	ASP	A	108	32.282	65.144	87.947	1.00	16.92
ATOM	752	CG	ASP	A	108	32.862	66.530	88.143	1.00	21.34
ATOM	753	OD1	ASP	A	108	32.247	67.528	87.812	1.00	23.69
ATOM	754	OD2	ASP	A	108	33.983	66.642	88.614	1.00	27.32
ATOM	755	N	LEU	A	109	33.049	65.065	85.107	1.00	18.48
ATOM	756	CA	LEU	A	109	33.814	65.703	84.005	1.00	20.77



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ATOM	757	C	LEU A 109	32.954	65.922	82.752	1.00	21.46
ATOM	758	O	LEU A 109	32.905	67.026	82.199	1.00	23.24
ATOM	759	CB	LEU A 109	35.024	64.826	83.679	1.00	20.60
ATOM	760	CG	LEU A 109	36.393	65.285	84.113	1.00	21.65
ATOM	761	CD1	LEU A 109	37.408	64.213	84.096	1.00	17.20
ATOM	762	CD2	LEU A 109	36.469	66.186	85.254	1.00	20.25
ATOM	763	N	ALA A 110	32.206	64.812	82.422	1.00	21.81
ATOM	764	CA	ALA A 110	31.336	64.771	81.215	1.00	20.79
ATOM	765	C	ALA A 110	30.074	65.608	81.232	1.00	23.23
ATOM	766	O	ALA A 110	29.504	65.885	80.182	1.00	23.66
ATOM	767	CB	ALA A 110	30.921	63.333	80.868	1.00	20.49
ATOM	768	N	THR A 111	29.672	66.038	82.465	1.00	20.15
ATOM	769	CA	THR A 111	28.453	66.863	82.653	1.00	19.21
ATOM	770	C	THR A 111	28.654	68.292	83.132	1.00	18.58
ATOM	771	O	THR A 111	27.754	69.106	83.131	1.00	18.77
ATOM	772	CB	THR A 111	27.469	66.257	83.628	1.00	18.46
ATOM	773	OG1	THR A 111	28.011	66.399	84.949	1.00	23.25
ATOM	774	CG2	THR A 111	27.094	64.802	83.347	1.00	15.78
ATOM	775	N	ARG A 112	29.870	68.595	83.547	1.00	20.94
ATOM	776	CA	ARG A 112	30.068	69.805	84.369	1.00	22.62
ATOM	777	C	ARG A 112	29.745	71.185	83.786	1.00	23.68
ATOM	778	O	ARG A 112	29.035	72.025	84.325	1.00	21.09
ATOM	779	CB	ARG A 112	31.512	69.782	84.911	1.00	22.88
ATOM	780	CG	ARG A 112	31.847	70.852	85.952	1.00	22.67
ATOM	781	CD	ARG A 112	33.319	70.922	86.319	1.00	18.55
ATOM	782	NE	ARG A 112	33.831	69.709	86.930	1.00	22.11
ATOM	783	CZ	ARG A 112	35.138	69.496	86.853	1.00	21.99
ATOM	784	NH1	ARG A 112	35.949	70.322	86.227	1.00	23.29
ATOM	785	NH2	ARG A 112	35.623	68.436	87.414	1.00	23.83
ATOM	786	N	SER A 113	30.323	71.398	82.583	1.00	21.66
ATOM	787	CA	SER A 113	30.146	72.736	81.981	1.00	19.14
ATOM	788	C	SER A 113	28.721	73.124	81.629	1.00	20.09
ATOM	789	O	SER A 113	28.288	74.263	81.806	1.00	23.06
ATOM	790	CB	SER A 113	31.029	72.919	80.732	1.00	24.64
ATOM	791	OG	SER A 113	30.812	71.854	79.778	1.00	25.18
ATOM	792	N	ALA A 114	27.955	72.094	81.186	1.00	19.43
ATOM	793	CA	ALA A 114	26.510	72.272	80.944	1.00	17.15
ATOM	794	C	ALA A 114	25.695	72.377	82.247	1.00	16.95
ATOM	795	O	ALA A 114	24.890	73.293	82.402	1.00	17.79
ATOM	796	CB	ALA A 114	25.935	71.096	80.117	1.00	15.05
ATOM	797	N	LYS A 115	25.993	71.462	83.200	1.00	18.76
ATOM	798	CA	LYS A 115	25.431	71.618	84.559	1.00	20.52
ATOM	799	C	LYS A 115	25.524	73.029	85.143	1.00	18.24
ATOM	800	O	LYS A 115	24.535	73.710	85.429	1.00	19.61
ATOM	801	CB	LYS A 115	26.048	70.606	85.508	1.00	17.41
ATOM	802	CG	LYS A 115	25.304	69.294	85.482	1.00	22.93
ATOM	803	CD	LYS A 115	25.867	68.477	86.654	1.00	26.73
ATOM	804	CE	LYS A 115	25.353	67.039	86.850	1.00	26.14
ATOM	805	NZ	LYS A 115	23.888	67.023	87.009	1.00	26.36
ATOM	806	N	ASP A 116	26.784	73.454	85.203	1.00	19.25
ATOM	807	CA	ASP A 116	27.073	74.739	85.832	1.00	20.02
ATOM	808	C	ASP A 116	26.589	75.938	85.076	1.00	23.51
ATOM	809	O	ASP A 116	26.208	76.967	85.612	1.00	24.69
ATOM	810	CB	ASP A 116	28.573	74.896	86.053	1.00	22.26

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ATOM	811	CG	ASP	A	116	29.203	73.871	87.029	1.00	25.80
ATOM	812	OD1	ASP	A	116	28.502	73.085	87.657	1.00	27.77
ATOM	813	OD2	ASP	A	116	30.431	73.847	87.166	1.00	28.44
ATOM	814	N	HIS	A	117	26.596	75.793	83.741	1.00	23.53
ATOM	815	CA	HIS	A	117	26.022	76.894	82.957	1.00	21.71
ATOM	816	C	HIS	A	117	24.496	77.044	83.026	1.00	20.75
ATOM	817	O	HIS	A	117	23.932	78.108	83.223	1.00	20.51
ATOM	818	CB	HIS	A	117	26.536	76.787	81.501	1.00	22.93
ATOM	819	CG	HIS	A	117	25.987	77.909	80.635	1.00	22.08
ATOM	820	ND1	HIS	A	117	26.531	79.128	80.459	1.00	23.33
ATOM	821	CD2	HIS	A	117	24.824	77.852	79.881	1.00	22.30
ATOM	822	CE1	HIS	A	117	25.741	79.836	79.615	1.00	23.49
ATOM	823	NE2	HIS	A	117	24.693	79.041	79.262	1.00	23.57
ATOM	824	N	TYR	A	118	23.825	75.906	82.825	1.00	19.95
ATOM	825	CA	TYR	A	118	22.363	76.013	82.795	1.00	19.91
ATOM	826	C	TYR	A	118	21.711	76.075	84.159	1.00	22.89
ATOM	827	O	TYR	A	118	20.615	76.596	84.278	1.00	22.53
ATOM	828	CB	TYR	A	118	21.702	74.869	82.020	1.00	18.70
ATOM	829	CG	TYR	A	118	22.112	74.964	80.550	1.00	19.86
ATOM	830	CD1	TYR	A	118	21.604	76.030	79.775	1.00	20.81
ATOM	831	CD2	TYR	A	118	22.998	74.004	80.005	1.00	20.19
ATOM	832	CE1	TYR	A	118	21.964	76.104	78.410	1.00	24.18
ATOM	833	CE2	TYR	A	118	23.393	74.097	78.652	1.00	22.07
ATOM	834	CZ	TYR	A	118	22.841	75.133	77.869	1.00	24.85
ATOM	835	OH	TYR	A	118	23.138	75.231	76.525	1.00	25.02
ATOM	836	N	MET	A	119	22.385	75.453	85.158	1.00	22.72
ATOM	837	CA	MET	A	119	21.795	75.408	86.516	1.00	25.49
ATOM	838	C	MET	A	119	20.328	75.033	86.619	1.00	22.79
ATOM	839	O	MET	A	119	19.526	75.639	87.309	1.00	23.65
ATOM	840	CB	MET	A	119	22.009	76.758	87.200	1.00	31.90
ATOM	841	CG	MET	A	119	23.479	77.200	87.296	1.00	41.79
ATOM	842	SD	MET	A	119	23.683	78.779	88.163	1.00	50.25
ATOM	843	CE	MET	A	119	22.932	79.838	86.910	1.00	48.37
ATOM	844	N	ARG	A	120	19.958	74.021	85.840	1.00	21.05
ATOM	845	CA	ARG	A	120	18.529	73.782	85.704	1.00	19.45
ATOM	846	C	ARG	A	120	17.877	73.247	86.989	1.00	16.34
ATOM	847	O	ARG	A	120	18.483	72.369	87.587	1.00	17.21
ATOM	848	CB	ARG	A	120	18.345	72.757	84.558	1.00	16.25
ATOM	849	CG	ARG	A	120	16.913	72.517	84.063	1.00	17.39
ATOM	850	CD	ARG	A	120	16.775	71.558	82.842	1.00	19.83
ATOM	851	NE	ARG	A	120	15.450	71.636	82.189	1.00	20.39
ATOM	852	CZ	ARG	A	120	14.929	70.642	81.479	1.00	12.14
ATOM	853	NH1	ARG	A	120	15.600	69.574	81.259	1.00	12.74
ATOM	854	NH2	ARG	A	120	13.724	70.767	81.007	1.00	15.75
ATOM	855	N	ILE	A	121	16.676	73.723	87.290	1.00	16.46
ATOM	856	CA	ILE	A	121	15.807	73.186	88.360	1.00	22.91
ATOM	857	C	ILE	A	121	15.258	71.795	88.080	1.00	23.50
ATOM	858	O	ILE	A	121	14.648	71.571	87.043	1.00	26.14
ATOM	859	CB	ILE	A	121	14.594	74.134	88.686	1.00	25.98
ATOM	860	CG1	ILE	A	121	14.986	75.592	88.783	1.00	29.16
ATOM	861	CG2	ILE	A	121	13.793	73.870	89.982	1.00	23.20
ATOM	862	CD1	ILE	A	121	16.075	75.914	89.785	1.00	29.73
ATOM	863	N	ARG	A	122	15.463	70.877	89.036	1.00	21.01
ATOM	864	CA	ARG	A	122	14.883	69.534	88.976	1.00	19.80

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ATOM	865	C	ARG A 122	13.372	69.532	89.091	1.00	17.61
ATOM	866	O	ARG A 122	12.805	70.488	89.613	1.00	18.79
ATOM	867	CB	ARG A 122	15.533	68.653	90.033	1.00	17.47
ATOM	868	CG	ARG A 122	17.023	68.706	89.841	1.00	18.78
ATOM	869	CD	ARG A 122	17.721	67.861	90.852	1.00	21.00
ATOM	870	NE	ARG A 122	19.141	68.121	90.748	1.00	28.80
ATOM	871	CZ	ARG A 122	19.914	67.081	90.491	1.00	34.31
ATOM	872	NH1	ARG A 122	19.401	65.871	90.426	1.00	40.28
ATOM	873	NH2	ARG A 122	21.196	67.257	90.289	1.00	32.47
ATOM	874	N	PRO A 123	12.700	68.460	88.577	1.00	17.64
ATOM	875	CA	PRO A 123	11.243	68.461	88.684	1.00	18.56
ATOM	876	C	PRO A 123	10.668	68.630	90.118	1.00	20.86
ATOM	877	O	PRO A 123	9.881	69.536	90.331	1.00	20.65
ATOM	878	CB	PRO A 123	10.808	67.150	88.004	1.00	16.86
ATOM	879	CG	PRO A 123	12.028	66.572	87.296	1.00	15.55
ATOM	880	CD	PRO A 123	13.235	67.291	87.881	1.00	15.48
ATOM	881	N	PHE A 124	11.077	67.771	91.105	1.00	21.82
ATOM	882	CA	PHE A 124	10.489	67.948	92.468	1.00	20.01
ATOM	883	C	PHE A 124	10.541	69.394	93.016	1.00	16.73
ATOM	884	O	PHE A 124	9.581	69.970	93.486	1.00	17.82
ATOM	885	CB	PHE A 124	11.044	66.869	93.422	1.00	17.84
ATOM	886	CG	PHE A 124	12.484	67.199	93.795	1.00	19.87
ATOM	887	CD1	PHE A 124	12.748	68.117	94.850	1.00	20.96
ATOM	888	CD2	PHE A 124	13.554	66.632	93.075	1.00	19.87
ATOM	889	CE1	PHE A 124	14.068	68.524	95.134	1.00	21.78
ATOM	890	CE2	PHE A 124	14.881	67.014	93.381	1.00	21.98
ATOM	891	CZ	PHE A 124	15.129	67.975	94.386	1.00	23.27
ATOM	892	N	ALA A 125	11.681	70.039	92.775	1.00	18.30
ATOM	893	CA	ALA A 125	11.866	71.464	93.089	1.00	20.06
ATOM	894	C	ALA A 125	11.033	72.481	92.291	1.00	24.90
ATOM	895	O	ALA A 125	10.455	73.445	92.789	1.00	24.77
ATOM	896	CB	ALA A 125	13.358	71.840	92.990	1.00	16.96
ATOM	897	N	PHE A 126	10.941	72.202	90.977	1.00	23.91
ATOM	898	CA	PHE A 126	10.017	72.958	90.145	1.00	22.66
ATOM	899	C	PHE A 126	8.590	72.919	90.692	1.00	20.74
ATOM	900	O	PHE A 126	7.910	73.945	90.785	1.00	21.66
ATOM	901	CB	PHE A 126	10.051	72.379	88.705	1.00	19.61
ATOM	902	CG	PHE A 126	9.147	73.140	87.765	1.00	16.99
ATOM	903	CD1	PHE A 126	9.669	74.211	87.022	1.00	15.15
ATOM	904	CD2	PHE A 126	7.794	72.757	87.656	1.00	17.75
ATOM	905	CE1	PHE A 126	8.824	74.913	86.144	1.00	14.16
ATOM	906	CE2	PHE A 126	6.940	73.472	86.799	1.00	17.56
ATOM	907	CZ	PHE A 126	7.471	74.538	86.048	1.00	12.93
ATOM	908	N	TYR A 127	8.183	71.664	91.002	1.00	20.13
ATOM	909	CA	TYR A 127	6.843	71.414	91.525	1.00	20.41
ATOM	910	C	TYR A 127	6.642	71.689	93.032	1.00	24.41
ATOM	911	O	TYR A 127	5.525	71.665	93.532	1.00	23.70
ATOM	912	CB	TYR A 127	6.370	69.994	91.207	1.00	20.85
ATOM	913	CG	TYR A 127	6.198	69.850	89.697	1.00	25.51
ATOM	914	CD1	TYR A 127	7.200	69.185	88.947	1.00	27.02
ATOM	915	CD2	TYR A 127	5.064	70.407	89.065	1.00	25.24
ATOM	916	CE1	TYR A 127	7.057	69.037	87.552	1.00	28.75
ATOM	917	CE2	TYR A 127	4.907	70.261	87.663	1.00	28.24
ATOM	918	CZ	TYR A 127	5.891	69.543	86.936	1.00	28.76

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ATOM	919	OH	TYR A 127	5.716	69.314	85.588	1.00	27.53
ATOM	920	N	GLY A 128	7.764	71.960	93.723	1.00	23.74
ATOM	921	CA	GLY A 128	7.675	72.217	95.170	1.00	24.88
ATOM	922	C	GLY A 128	7.138	71.011	95.924	1.00	24.57
ATOM	923	O	GLY A 128	6.383	71.095	96.866	1.00	29.82
ATOM	924	N	VAL A 129	7.527	69.854	95.426	1.00	24.16
ATOM	925	CA	VAL A 129	7.144	68.604	96.044	1.00	23.21
ATOM	926	C	VAL A 129	8.377	67.802	96.358	1.00	24.99
ATOM	927	O	VAL A 129	9.529	68.188	96.189	1.00	25.90
ATOM	928	CB	VAL A 129	6.193	67.776	95.187	1.00	22.38
ATOM	929	CG1	VAL A 129	6.738	67.390	93.815	1.00	17.75
ATOM	930	CG2	VAL A 129	4.895	68.549	95.125	1.00	24.52
ATOM	931	N	SER A 130	8.089	66.617	96.832	1.00	25.98
ATOM	932	CA	SER A 130	9.242	65.724	96.973	1.00	29.71
ATOM	933	C	SER A 130	9.322	64.672	95.895	1.00	29.73
ATOM	934	O	SER A 130	8.403	64.485	95.103	1.00	30.28
ATOM	935	CB	SER A 130	9.183	64.999	98.309	1.00	35.36
ATOM	936	OG	SER A 130	7.964	64.244	98.427	1.00	41.61
ATOM	937	N	THR A 131	10.440	63.952	95.934	1.00	30.35
ATOM	938	CA	THR A 131	10.533	62.819	94.996	1.00	27.90
ATOM	939	C	THR A 131	9.733	61.569	95.361	1.00	28.80
ATOM	940	O	THR A 131	9.051	61.508	96.366	1.00	30.16
ATOM	941	CB	THR A 131	11.996	62.471	94.783	1.00	26.62
ATOM	942	OG1	THR A 131	12.500	61.841	95.953	1.00	29.21
ATOM	943	CG2	THR A 131	12.839	63.682	94.446	1.00	19.32
ATOM	944	N	CYS A 132	9.835	60.528	94.551	1.00	27.12
ATOM	945	CA	CYS A 132	9.203	59.271	94.996	1.00	27.75
ATOM	946	C	CYS A 132	9.911	58.540	96.137	1.00	28.96
ATOM	947	O	CYS A 132	9.556	57.487	96.634	1.00	28.80
ATOM	948	CB	CYS A 132	9.081	58.274	93.831	1.00	24.68
ATOM	949	SG	CYS A 132	10.538	57.273	93.459	1.00	24.12
ATOM	950	N	ASN A 133	11.021	59.158	96.447	1.00	33.31
ATOM	951	CA	ASN A 133	12.012	58.492	97.236	1.00	39.44
ATOM	952	C	ASN A 133	12.008	58.776	98.750	1.00	45.19
ATOM	953	O	ASN A 133	12.269	57.928	99.583	1.00	50.38
ATOM	954	CB	ASN A 133	13.285	58.876	96.522	1.00	35.83
ATOM	955	CG	ASN A 133	14.294	57.823	96.731	1.00	37.18
ATOM	956	OD1	ASN A 133	15.478	58.059	96.663	1.00	38.83
ATOM	957	ND2	ASN A 133	13.815	56.623	97.017	1.00	42.51
ATOM	958	N	THR A 134	11.642	59.993	99.118	1.00	48.69
ATOM	959	CA	THR A 134	12.585	61.110	98.925	1.00	56.17
ATOM	960	C	THR A 134	13.935	61.171	99.735	1.00	61.49
ATOM	961	OCT1	THR A 134	14.052	60.565	100.816	1.00	66.36
ATOM	962	OCT2	THR A 134	14.937	61.779	99.291	1.00	63.18
ATOM	963	CB	THR A 134	11.704	62.374	98.968	1.00	56.04
ATOM	964	OG1	THR A 134	12.306	63.614	98.469	1.00	56.23
ATOM	965	CG2	THR A 134	10.869	62.400	100.243	1.00	53.77
ATOM	966	N	GLN A 137	16.953	60.437	100.819	1.00	100.00
ATOM	967	CA	GLN A 137	17.845	60.498	102.027	1.00	99.78
ATOM	968	C	GLN A 137	19.036	61.512	102.211	1.00	98.61
ATOM	969	O	GLN A 137	19.386	61.891	103.324	1.00	97.54
ATOM	970	CB	GLN A 137	18.343	59.083	102.397	1.00	100.00
ATOM	971	CG	GLN A 137	17.669	58.407	103.615	1.00	99.38
ATOM	972	CD	GLN A 137	18.060	59.017	104.963	1.00	98.64

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ATOM	973	OE1	GLN	A	137	17.484	58.784	106.009	1.00	98.03
ATOM	974	NE2	GLN	A	137	19.086	59.847	104.972	1.00	100.00
ATOM	975	N	ASP	A	138	19.627	61.949	101.081	1.00	97.91
ATOM	976	CA	ASP	A	138	20.479	63.151	101.162	1.00	95.99
ATOM	977	C	ASP	A	138	19.761	64.494	101.063	1.00	93.86
ATOM	978	O	ASP	A	138	18.589	64.579	100.711	1.00	92.76
ATOM	979	CB	ASP	A	138	21.585	63.102	100.115	1.00	97.46
ATOM	980	CG	ASP	A	138	22.893	62.963	100.866	1.00	100.00
ATOM	981	OD1	ASP	A	138	23.371	61.842	101.028	1.00	100.00
ATOM	982	OD2	ASP	A	138	23.432	63.969	101.333	1.00	100.00
ATOM	983	N	LYS	A	139	20.494	65.564	101.380	1.00	92.69
ATOM	984	CA	LYS	A	139	19.813	66.855	101.218	1.00	91.50
ATOM	985	C	LYS	A	139	19.719	67.313	99.775	1.00	88.92
ATOM	986	O	LYS	A	139	20.557	68.082	99.308	1.00	89.47
ATOM	987	CB	LYS	A	139	20.464	67.987	102.010	1.00	94.21
ATOM	988	CG	LYS	A	139	19.574	69.246	102.020	1.00	96.82
ATOM	989	CD	LYS	A	139	20.362	70.569	102.123	1.00	99.43
ATOM	990	CE	LYS	A	139	20.785	71.241	100.793	1.00	100.00
ATOM	991	NZ	LYS	A	139	21.686	70.402	99.978	1.00	100.00
ATOM	992	N	LEU	A	140	18.654	66.828	99.114	1.00	85.87
ATOM	993	CA	LEU	A	140	18.426	67.018	97.660	1.00	79.60
ATOM	994	C	LEU	A	140	18.772	68.392	97.043	1.00	75.62
ATOM	995	O	LEU	A	140	18.242	69.442	97.416	1.00	75.74
ATOM	996	CB	LEU	A	140	16.981	66.620	97.283	1.00	77.27
ATOM	997	CG	LEU	A	140	16.640	65.142	97.462	1.00	74.31
ATOM	998	CD1	LEU	A	140	17.569	64.263	96.645	1.00	73.21
ATOM	999	CD2	LEU	A	140	15.178	64.838	97.167	1.00	73.91
ATOM	1000	N	SER	A	141	19.713	68.357	96.067	1.00	70.08
ATOM	1001	CA	SER	A	141	19.868	69.619	95.320	1.00	64.86
ATOM	1002	C	SER	A	141	18.713	69.941	94.396	1.00	61.18
ATOM	1003	O	SER	A	141	18.189	69.080	93.708	1.00	61.77
ATOM	1004	CB	SER	A	141	21.127	69.682	94.461	1.00	64.49
ATOM	1005	OG	SER	A	141	21.354	71.028	94.002	1.00	66.43
ATOM	1006	N	LYS	A	142	18.349	71.235	94.379	1.00	57.81
ATOM	1007	CA	LYS	A	142	17.238	71.661	93.493	1.00	54.35
ATOM	1008	C	LYS	A	142	17.498	71.829	91.964	1.00	45.94
ATOM	1009	O	LYS	A	142	16.615	72.091	91.202	1.00	40.89
ATOM	1010	CB	LYS	A	142	16.631	72.953	94.061	1.00	57.69
ATOM	1011	CG	LYS	A	142	17.518	74.222	93.959	1.00	62.63
ATOM	1012	CD	LYS	A	142	16.625	75.420	93.545	1.00	68.07
ATOM	1013	CE	LYS	A	142	17.200	76.856	93.475	1.00	71.28
ATOM	1014	NZ	LYS	A	142	16.136	77.844	93.162	1.00	70.88
ATOM	1015	N	ASN	A	143	18.772	71.719	91.611	1.00	45.99
ATOM	1016	CA	ASN	A	143	19.527	72.392	90.538	1.00	44.71
ATOM	1017	C	ASN	A	143	20.592	71.481	89.878	1.00	42.57
ATOM	1018	O	ASN	A	143	20.794	70.322	90.283	1.00	40.17
ATOM	1019	CB	ASN	A	143	20.343	73.547	91.124	1.00	50.34
ATOM	1020	CG	ASN	A	143	19.624	74.818	90.876	1.00	55.19
ATOM	1021	OD1	ASN	A	143	18.441	74.944	91.098	1.00	59.21
ATOM	1022	ND2	ASN	A	143	20.366	75.786	90.389	1.00	59.88
ATOM	1023	N	GLY	A	144	21.265	72.084	88.819	1.00	39.72
ATOM	1024	CA	GLY	A	144	22.264	71.401	87.958	1.00	26.74
ATOM	1025	C	GLY	A	144	21.691	70.105	87.407	1.00	21.44
ATOM	1026	O	GLY	A	144	22.343	69.071	87.322	1.00	25.78

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ATOM	1027	N	SER A 145	20.380	70.181	87.105	1.00	19.15
ATOM	1028	CA	SER A 145	19.590	69.023	86.596	1.00	20.14
ATOM	1029	C	SER A 145	20.077	68.461	85.223	1.00	20.58
ATOM	1030	O	SER A 145	20.121	67.279	84.943	1.00	21.22
ATOM	1031	CB	SER A 145	18.171	69.499	86.338	1.00	18.89
ATOM	1032	OG	SER A 145	17.219	68.526	86.712	1.00	28.02
ATOM	1033	N	TYR A 146	20.531	69.419	84.399	1.00	22.70
ATOM	1034	CA	TYR A 146	20.867	69.170	82.968	1.00	19.51
ATOM	1035	C	TYR A 146	22.366	69.260	82.633	1.00	16.00
ATOM	1036	O	TYR A 146	22.930	70.339	82.736	1.00	17.85
ATOM	1037	CB	TYR A 146	20.097	70.216	82.114	1.00	18.79
ATOM	1038	CG	TYR A 146	20.211	69.933	80.600	1.00	20.29
ATOM	1039	CD1	TYR A 146	19.310	69.027	80.015	1.00	19.58
ATOM	1040	CD2	TYR A 146	21.205	70.582	79.824	1.00	20.42
ATOM	1041	CE1	TYR A 146	19.389	68.781	78.631	1.00	23.13
ATOM	1042	CE2	TYR A 146	21.287	70.337	78.424	1.00	21.68
ATOM	1043	CZ	TYR A 146	20.349	69.449	77.849	1.00	20.03
ATOM	1044	OH	TYR A 146	20.320	69.236	76.483	1.00	21.40
ATOM	1045	N	PRO A 147	22.994	68.144	82.187	1.00	16.52
ATOM	1046	CA	PRO A 147	22.385	66.793	82.188	1.00	17.87
ATOM	1047	C	PRO A 147	22.496	66.069	83.580	1.00	20.67
ATOM	1048	O	PRO A 147	23.198	66.531	84.480	1.00	22.35
ATOM	1049	CB	PRO A 147	23.250	66.107	81.122	1.00	15.36
ATOM	1050	CG	PRO A 147	24.649	66.716	81.297	1.00	15.06
ATOM	1051	CD	PRO A 147	24.356	68.168	81.630	1.00	16.28
ATOM	1052	N	SER A 148	21.827	64.908	83.662	1.00	18.73
ATOM	1053	CA	SER A 148	21.951	64.019	84.823	1.00	19.51
ATOM	1054	C	SER A 148	23.269	63.281	84.930	1.00	19.93
ATOM	1055	O	SER A 148	23.601	62.439	84.108	1.00	20.09
ATOM	1056	CB	SER A 148	20.828	62.997	84.807	1.00	18.55
ATOM	1057	OG	SER A 148	20.990	61.966	85.780	1.00	19.29
ATOM	1058	N	GLY A 149	24.036	63.618	85.972	1.00	18.26
ATOM	1059	CA	GLY A 149	25.284	62.888	86.231	1.00	16.00
ATOM	1060	C	GLY A 149	25.096	61.411	86.577	1.00	19.38
ATOM	1061	O	GLY A 149	25.791	60.549	86.044	1.00	21.04
ATOM	1062	N	HIS A 150	24.085	61.096	87.427	1.00	20.25
ATOM	1063	CA	HIS A 150	23.690	59.680	87.624	1.00	19.01
ATOM	1064	C	HIS A 150	23.381	58.861	86.330	1.00	19.93
ATOM	1065	O	HIS A 150	23.833	57.725	86.145	1.00	20.78
ATOM	1066	CB	HIS A 150	22.507	59.533	88.619	1.00	18.01
ATOM	1067	CG	HIS A 150	22.162	58.068	88.909	1.00	20.60
ATOM	1068	ND1	HIS A 150	22.864	57.235	89.730	1.00	23.41
ATOM	1069	CD2	HIS A 150	21.117	57.313	88.374	1.00	21.91
ATOM	1070	CE1	HIS A 150	22.287	55.996	89.732	1.00	22.83
ATOM	1071	NE2	HIS A 150	21.220	56.051	88.893	1.00	24.19
ATOM	1072	N	THR A 151	22.593	59.482	85.432	1.00	18.98
ATOM	1073	CA	THR A 151	22.325	58.814	84.132	1.00	17.17
ATOM	1074	C	THR A 151	23.548	58.652	83.228	1.00	13.61
ATOM	1075	O	THR A 151	23.814	57.594	82.659	1.00	17.00
ATOM	1076	CB	THR A 151	21.270	59.590	83.407	1.00	16.57
ATOM	1077	OG1	THR A 151	20.137	59.738	84.258	1.00	18.00
ATOM	1078	CG2	THR A 151	20.898	58.983	82.045	1.00	13.22
ATOM	1079	N	SER A 152	24.361	59.722	83.197	1.00	14.30
ATOM	1080	CA	SER A 152	25.687	59.598	82.557	1.00	15.99

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ATOM	1081	C	SER A 152	26.575	58.446	83.029	1.00	19.72
ATOM	1082	O	SER A 152	27.086	57.628	82.255	1.00	17.38
ATOM	1083	CB	SER A 152	26.434	60.927	82.644	1.00	12.58
ATOM	1084	OG	SER A 152	27.648	60.861	81.911	1.00	16.08
ATOM	1085	N	ILE A 153	26.662	58.340	84.403	1.00	20.60
ATOM	1086	CA	ILE A 153	27.272	57.121	85.017	1.00	16.15
ATOM	1087	C	ILE A 153	26.622	55.802	84.631	1.00	10.76
ATOM	1088	O	ILE A 153	27.293	54.850	84.262	1.00	14.38
ATOM	1089	CB	ILE A 153	27.384	57.170	86.608	1.00	15.02
ATOM	1090	CG1	ILE A 153	28.187	58.421	86.963	1.00	16.37
ATOM	1091	CG2	ILE A 153	28.154	55.944	87.164	1.00	12.98
ATOM	1092	CD1	ILE A 153	27.870	59.034	88.338	1.00	16.58
ATOM	1093	N	GLY A 154	25.285	55.763	84.720	1.00	9.72
ATOM	1094	CA	GLY A 154	24.662	54.476	84.397	1.00	13.63
ATOM	1095	C	GLY A 154	24.843	54.033	82.910	1.00	16.00
ATOM	1096	O	GLY A 154	25.022	52.866	82.571	1.00	16.37
ATOM	1097	N	TRP A 155	24.801	55.047	82.025	1.00	16.77
ATOM	1098	CA	TRP A 155	24.960	54.747	80.589	1.00	16.73
ATOM	1099	C	TRP A 155	26.378	54.351	80.200	1.00	15.90
ATOM	1100	O	TRP A 155	26.656	53.301	79.628	1.00	18.41
ATOM	1101	CB	TRP A 155	24.442	55.940	79.771	1.00	16.52
ATOM	1102	CG	TRP A 155	24.320	55.475	78.321	1.00	19.11
ATOM	1103	CD1	TRP A 155	25.009	56.015	77.210	1.00	18.94
ATOM	1104	CD2	TRP A 155	23.471	54.426	77.765	1.00	18.98
ATOM	1105	NE1	TRP A 155	24.679	55.352	76.044	1.00	17.77
ATOM	1106	CE2	TRP A 155	23.781	54.322	76.357	1.00	22.22
ATOM	1107	CE3	TRP A 155	22.585	53.486	78.337	1.00	19.43
ATOM	1108	CZ2	TRP A 155	23.084	53.377	75.564	1.00	17.99
ATOM	1109	CZ3	TRP A 155	21.913	52.538	77.537	1.00	19.46
ATOM	1110	CH2	TRP A 155	22.191	52.464	76.158	1.00	17.84
ATOM	1111	N	ALA A 156	27.299	55.209	80.623	1.00	15.37
ATOM	1112	CA	ALA A 156	28.702	54.836	80.515	1.00	14.36
ATOM	1113	C	ALA A 156	29.156	53.503	81.108	1.00	19.46
ATOM	1114	O	ALA A 156	29.895	52.723	80.528	1.00	19.86
ATOM	1115	CB	ALA A 156	29.564	55.918	81.136	1.00	15.83
ATOM	1116	N	THR A 157	28.651	53.207	82.327	1.00	19.95
ATOM	1117	CA	THR A 157	28.820	51.832	82.831	1.00	17.52
ATOM	1118	C	THR A 157	28.177	50.744	81.994	1.00	15.22
ATOM	1119	O	THR A 157	28.825	49.745	81.765	1.00	19.09
ATOM	1120	CB	THR A 157	28.328	51.667	84.291	1.00	14.92
ATOM	1121	OG1	THR A 157	28.932	52.679	85.054	1.00	18.29
ATOM	1122	CG2	THR A 157	28.620	50.327	84.944	1.00	13.21
ATOM	1123	N	ALA A 158	26.930	50.947	81.535	1.00	14.63
ATOM	1124	CA	ALA A 158	26.365	49.936	80.621	1.00	17.10
ATOM	1125	C	ALA A 158	27.213	49.686	79.354	1.00	15.52
ATOM	1126	O	ALA A 158	27.539	48.565	79.025	1.00	16.52
ATOM	1127	CB	ALA A 158	24.942	50.300	80.203	1.00	13.99
ATOM	1128	N	LEU A 159	27.655	50.766	78.705	1.00	17.91
ATOM	1129	CA	LEU A 159	28.613	50.615	77.580	1.00	17.69
ATOM	1130	C	LEU A 159	29.895	49.851	77.846	1.00	19.93
ATOM	1131	O	LEU A 159	30.277	48.954	77.092	1.00	19.21
ATOM	1132	CB	LEU A 159	28.959	51.971	76.939	1.00	14.08
ATOM	1133	CG	LEU A 159	27.744	52.759	76.396	1.00	11.97
ATOM	1134	CD1	LEU A 159	27.045	52.105	75.210	1.00	12.90

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ATOM	1135	CD2	LEU	A	159	28.177	54.158	76.046	1.00	12.40
ATOM	1136	N	VAL	A	160	30.547	50.181	79.014	1.00	21.70
ATOM	1137	CA	VAL	A	160	31.713	49.315	79.310	1.00	20.85
ATOM	1138	C	VAL	A	160	31.429	47.877	79.767	1.00	21.33
ATOM	1139	O	VAL	A	160	32.086	46.918	79.409	1.00	20.74
ATOM	1140	CB	VAL	A	160	32.574	50.032	80.367	1.00	21.59
ATOM	1141	CG1	VAL	A	160	33.518	49.143	81.174	1.00	20.11
ATOM	1142	CG2	VAL	A	160	33.299	51.307	79.977	1.00	20.10
ATOM	1143	N	LEU	A	161	30.351	47.711	80.542	1.00	21.86
ATOM	1144	CA	LEU	A	161	29.850	46.366	80.838	1.00	20.50
ATOM	1145	C	LEU	A	161	29.462	45.490	79.613	1.00	23.16
ATOM	1146	O	LEU	A	161	29.753	44.294	79.564	1.00	22.89
ATOM	1147	CB	LEU	A	161	28.623	46.472	81.733	1.00	18.65
ATOM	1148	CG	LEU	A	161	28.685	46.438	83.262	1.00	20.99
ATOM	1149	CD1	LEU	A	161	27.473	46.378	84.194	1.00	21.43
ATOM	1150	CD2	LEU	A	161	29.729	45.492	83.855	1.00	19.30
ATOM	1151	N	ALA	A	162	28.755	46.146	78.648	1.00	21.20
ATOM	1152	CA	ALA	A	162	28.384	45.496	77.361	1.00	19.14
ATOM	1153	C	ALA	A	162	29.591	44.948	76.586	1.00	17.15
ATOM	1154	O	ALA	A	162	29.620	43.812	76.133	1.00	20.85
ATOM	1155	CB	ALA	A	162	27.581	46.464	76.500	1.00	17.38
ATOM	1156	N	GLU	A	163	30.663	45.745	76.603	1.00	14.74
ATOM	1157	CA	GLU	A	163	31.962	45.262	76.118	1.00	17.48
ATOM	1158	C	GLU	A	163	32.648	44.080	76.824	1.00	22.07
ATOM	1159	O	GLU	A	163	33.271	43.216	76.227	1.00	23.96
ATOM	1160	CB	GLU	A	163	32.915	46.448	76.000	1.00	13.52
ATOM	1161	CG	GLU	A	163	34.227	46.018	75.359	1.00	13.04
ATOM	1162	CD	GLU	A	163	35.240	47.119	75.338	1.00	15.88
ATOM	1163	OE1	GLU	A	163	36.427	46.814	75.269	1.00	19.78
ATOM	1164	OE2	GLU	A	163	34.873	48.290	75.377	1.00	20.10
ATOM	1165	N	ILE	A	164	32.504	44.039	78.153	1.00	20.17
ATOM	1166	CA	ILE	A	164	32.996	42.869	78.905	1.00	18.72
ATOM	1167	C	ILE	A	164	32.164	41.609	78.757	1.00	17.39
ATOM	1168	O	ILE	A	164	32.635	40.481	78.674	1.00	20.44
ATOM	1169	CB	ILE	A	164	33.132	43.293	80.382	1.00	20.67
ATOM	1170	CG1	ILE	A	164	34.222	44.361	80.452	1.00	18.83
ATOM	1171	CG2	ILE	A	164	33.398	42.110	81.345	1.00	20.70
ATOM	1172	CD1	ILE	A	164	34.144	45.084	81.793	1.00	21.31
ATOM	1173	N	ASN	A	165	30.869	41.846	78.704	1.00	18.41
ATOM	1174	CA	ASN	A	165	29.979	40.712	78.524	1.00	21.36
ATOM	1175	C	ASN	A	165	28.957	40.867	77.375	1.00	23.74
ATOM	1176	O	ASN	A	165	27.753	40.988	77.563	1.00	23.14
ATOM	1177	CB	ASN	A	165	29.324	40.404	79.878	1.00	21.69
ATOM	1178	CG	ASN	A	165	28.471	39.156	79.861	1.00	25.72
ATOM	1179	OD1	ASN	A	165	28.469	38.307	78.967	1.00	29.37
ATOM	1180	ND2	ASN	A	165	27.730	39.051	80.951	1.00	27.39
ATOM	1181	N	PRO	A	166	29.466	40.814	76.118	1.00	25.93
ATOM	1182	CA	PRO	A	166	28.556	40.971	74.957	1.00	26.27
ATOM	1183	C	PRO	A	166	27.447	39.924	74.837	1.00	24.06
ATOM	1184	O	PRO	A	166	26.361	40.184	74.360	1.00	24.11
ATOM	1185	CB	PRO	A	166	29.517	41.040	73.781	1.00	25.15
ATOM	1186	CG	PRO	A	166	30.731	40.254	74.255	1.00	27.68
ATOM	1187	CD	PRO	A	166	30.849	40.613	75.728	1.00	24.89
ATOM	1188	N	GLN	A	167	27.679	38.741	75.385	1.00	25.15



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ATOM	1189	CA	GLN A 167	26.552	37.804	75.508	1.00	27.09
ATOM	1190	C	GLN A 167	25.275	38.321	76.189	1.00	25.06
ATOM	1191	O	GLN A 167	24.162	37.932	75.883	1.00	23.75
ATOM	1192	CB	GLN A 167	27.080	36.617	76.282	1.00	35.50
ATOM	1193	CG	GLN A 167	27.386	35.380	75.468	1.00	52.12
ATOM	1194	CD	GLN A 167	26.074	34.747	75.000	1.00	65.78
ATOM	1195	OE1	GLN A 167	25.950	34.245	73.889	1.00	72.02
ATOM	1196	NE2	GLN A 167	25.047	34.780	75.867	1.00	71.50
ATOM	1197	N	ARG A 168	25.513	39.242	77.156	1.00	26.04
ATOM	1198	CA	ARG A 168	24.389	39.900	77.837	1.00	25.63
ATOM	1199	C	ARG A 168	24.242	41.368	77.558	1.00	23.88
ATOM	1200	O	ARG A 168	23.632	42.106	78.308	1.00	24.09
ATOM	1201	CB	ARG A 168	24.452	39.638	79.337	1.00	24.63
ATOM	1202	CG	ARG A 168	24.087	38.171	79.408	1.00	25.72
ATOM	1203	CD	ARG A 168	23.986	37.617	80.802	1.00	33.72
ATOM	1204	NE	ARG A 168	22.970	38.302	81.587	1.00	35.38
ATOM	1205	CZ	ARG A 168	21.729	37.877	81.680	1.00	35.91
ATOM	1206	NH1	ARG A 168	20.908	38.482	82.490	1.00	34.99
ATOM	1207	NH2	ARG A 168	21.314	36.867	80.975	1.00	39.28
ATOM	1208	N	GLN A 169	24.838	41.810	76.424	1.00	23.22
ATOM	1209	CA	GLN A 169	24.820	43.228	76.080	1.00	19.99
ATOM	1210	C	GLN A 169	23.441	43.850	76.067	1.00	21.38
ATOM	1211	O	GLN A 169	23.216	44.969	76.492	1.00	24.60
ATOM	1212	CB	GLN A 169	25.571	43.510	74.769	1.00	22.07
ATOM	1213	CG	GLN A 169	24.970	42.878	73.494	1.00	20.93
ATOM	1214	CD	GLN A 169	25.716	43.287	72.207	1.00	23.42
ATOM	1215	OE1	GLN A 169	26.680	44.055	72.202	1.00	24.82
ATOM	1216	NE2	GLN A 169	25.186	42.738	71.109	1.00	13.86
ATOM	1217	N	ASN A 170	22.455	43.089	75.600	1.00	20.48
ATOM	1218	CA	ASN A 170	21.138	43.736	75.525	1.00	20.97
ATOM	1219	C	ASN A 170	20.484	44.007	76.892	1.00	19.73
ATOM	1220	O	ASN A 170	19.852	45.020	77.128	1.00	18.90
ATOM	1221	CB	ASN A 170	20.195	42.930	74.595	1.00	24.43
ATOM	1222	CG	ASN A 170	20.763	42.881	73.153	1.00	25.82
ATOM	1223	OD1	ASN A 170	20.842	43.862	72.440	1.00	26.22
ATOM	1224	ND2	ASN A 170	21.197	41.709	72.734	1.00	25.47
ATOM	1225	N	GLU A 171	20.680	43.042	77.790	1.00	21.27
ATOM	1226	CA	GLU A 171	20.166	43.146	79.157	1.00	19.84
ATOM	1227	C	GLU A 171	20.849	44.220	79.926	1.00	16.23
ATOM	1228	O	GLU A 171	20.199	45.026	80.575	1.00	20.87
ATOM	1229	CB	GLU A 171	20.317	41.822	79.892	1.00	20.47
ATOM	1230	CG	GLU A 171	19.412	40.750	79.312	1.00	24.15
ATOM	1231	CD	GLU A 171	20.157	39.825	78.376	1.00	26.37
ATOM	1232	OE1	GLU A 171	21.076	40.256	77.685	1.00	23.54
ATOM	1233	OE2	GLU A 171	19.801	38.645	78.363	1.00	32.14
ATOM	1234	N	ILE A 172	22.169	44.236	79.751	1.00	17.53
ATOM	1235	CA	ILE A 172	23.029	45.318	80.257	1.00	16.90
ATOM	1236	C	ILE A 172	22.679	46.733	79.813	1.00	20.21
ATOM	1237	O	ILE A 172	22.454	47.636	80.617	1.00	18.91
ATOM	1238	CB	ILE A 172	24.507	44.992	79.956	1.00	17.00
ATOM	1239	CG1	ILE A 172	25.000	43.685	80.613	1.00	15.78
ATOM	1240	CG2	ILE A 172	25.426	46.163	80.300	1.00	18.13
ATOM	1241	CD1	ILE A 172	26.426	43.320	80.163	1.00	13.83
ATOM	1242	N	LEU A 173	22.575	46.909	78.468	1.00	20.75

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ATOM	1243	CA	LEU A 173	22.107	48.206	77.946	1.00	17.70
ATOM	1244	C	LEU A 173	20.699	48.622	78.396	1.00	16.26
ATOM	1245	O	LEU A 173	20.376	49.774	78.663	1.00	18.18
ATOM	1246	CB	LEU A 173	22.176	48.201	76.419	1.00	16.81
ATOM	1247	CG	LEU A 173	23.600	48.021	75.966	1.00	18.73
ATOM	1248	CD1	LEU A 173	24.410	49.282	76.138	1.00	16.97
ATOM	1249	CD2	LEU A 173	23.619	47.550	74.505	1.00	23.91
ATOM	1250	N	LYS A 174	19.835	47.625	78.475	1.00	15.86
ATOM	1251	CA	LYS A 174	18.494	47.970	78.945	1.00	19.21
ATOM	1252	C	LYS A 174	18.453	48.415	80.429	1.00	21.86
ATOM	1253	O	LYS A 174	17.800	49.404	80.737	1.00	20.00
ATOM	1254	CB	LYS A 174	17.577	46.773	78.700	1.00	20.19
ATOM	1255	CG	LYS A 174	16.094	47.130	78.731	1.00	27.84
ATOM	1256	CD	LYS A 174	15.799	48.368	77.858	1.00	36.14
ATOM	1257	CE	LYS A 174	14.309	48.628	77.774	1.00	40.56
ATOM	1258	NZ	LYS A 174	13.775	48.622	79.156	1.00	49.45
ATOM	1259	N	ARG A 175	19.250	47.698	81.286	1.00	21.93
ATOM	1260	CA	ARG A 175	19.476	48.145	82.686	1.00	19.65
ATOM	1261	C	ARG A 175	20.037	49.561	82.807	1.00	16.70
ATOM	1262	O	ARG A 175	19.476	50.419	83.468	1.00	18.12
ATOM	1263	CB	ARG A 175	20.345	47.126	83.467	1.00	21.25
ATOM	1264	CG	ARG A 175	20.608	47.477	84.954	1.00	22.00
ATOM	1265	CD	ARG A 175	19.259	47.669	85.656	1.00	25.63
ATOM	1266	NE	ARG A 175	19.435	47.923	87.095	1.00	29.77
ATOM	1267	CZ	ARG A 175	18.601	48.672	87.834	1.00	27.58
ATOM	1268	NH1	ARG A 175	17.550	49.301	87.355	1.00	24.74
ATOM	1269	NH2	ARG A 175	18.792	48.780	89.073	1.00	27.45
ATOM	1270	N	GLY A 176	21.122	49.800	82.048	1.00	17.53
ATOM	1271	CA	GLY A 176	21.698	51.143	81.893	1.00	17.18
ATOM	1272	C	GLY A 176	20.679	52.214	81.552	1.00	21.18
ATOM	1273	O	GLY A 176	20.582	53.278	82.149	1.00	21.85
ATOM	1274	N	TYR A 177	19.847	51.887	80.547	1.00	22.48
ATOM	1275	CA	TYR A 177	18.756	52.787	80.117	1.00	20.51
ATOM	1276	C	TYR A 177	17.754	53.106	81.242	1.00	18.92
ATOM	1277	O	TYR A 177	17.406	54.246	81.542	1.00	15.84
ATOM	1278	CB	TYR A 177	18.007	52.120	78.939	1.00	23.76
ATOM	1279	CG	TYR A 177	17.210	53.131	78.177	1.00	24.47
ATOM	1280	CD1	TYR A 177	15.817	53.306	78.397	1.00	26.61
ATOM	1281	CD2	TYR A 177	17.941	53.869	77.236	1.00	29.40
ATOM	1282	CE1	TYR A 177	15.139	54.308	77.661	1.00	29.08
ATOM	1283	CE2	TYR A 177	17.270	54.855	76.515	1.00	30.70
ATOM	1284	CZ	TYR A 177	15.899	55.092	76.747	1.00	32.01
ATOM	1285	OH	TYR A 177	15.401	56.167	76.020	1.00	41.52
ATOM	1286	N	GLU A 178	17.354	52.008	81.867	1.00	19.45
ATOM	1287	CA	GLU A 178	16.429	52.094	82.972	1.00	22.02
ATOM	1288	C	GLU A 178	16.820	52.802	84.236	1.00	20.09
ATOM	1289	O	GLU A 178	16.001	53.492	84.805	1.00	21.41
ATOM	1290	CB	GLU A 178	16.010	50.731	83.357	1.00	25.45
ATOM	1291	CG	GLU A 178	15.173	50.032	82.303	1.00	34.73
ATOM	1292	CD	GLU A 178	13.893	50.810	81.951	1.00	40.36
ATOM	1293	OE1	GLU A 178	13.432	51.667	82.707	1.00	33.51
ATOM	1294	OE2	GLU A 178	13.352	50.556	80.876	1.00	45.77
ATOM	1295	N	LEU A 179	18.090	52.695	84.609	1.00	19.63
ATOM	1296	CA	LEU A 179	18.655	53.567	85.665	1.00	19.10

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ATOM	1297	C	LEU A 179	18.366	55.051	85.511	1.00	20.25
ATOM	1298	O	LEU A 179	17.838	55.726	86.374	1.00	19.26
ATOM	1299	CB	LEU A 179	20.178	53.361	85.813	1.00	17.45
ATOM	1300	CG	LEU A 179	20.610	52.013	86.426	1.00	18.23
ATOM	1301	CD1	LEU A 179	20.093	51.829	87.873	1.00	16.98
ATOM	1302	CD2	LEU A 179	22.124	51.811	86.340	1.00	16.34
ATOM	1303	N	GLY A 180	18.647	55.545	84.290	1.00	19.84
ATOM	1304	CA	GLY A 180	18.171	56.903	83.987	1.00	15.90
ATOM	1305	C	GLY A 180	16.655	57.072	84.027	1.00	17.05
ATOM	1306	O	GLY A 180	16.130	58.031	84.564	1.00	19.49
ATOM	1307	N	GLN A 181	15.923	56.068	83.478	1.00	18.19
ATOM	1308	CA	GLN A 181	14.448	56.207	83.522	1.00	17.92
ATOM	1309	C	GLN A 181	13.822	56.265	84.938	1.00	18.20
ATOM	1310	O	GLN A 181	12.903	57.008	85.258	1.00	19.66
ATOM	1311	CB	GLN A 181	13.716	55.189	82.620	1.00	15.39
ATOM	1312	CG	GLN A 181	13.936	55.324	81.073	1.00	15.18
ATOM	1313	CD	GLN A 181	13.823	56.763	80.634	1.00	13.30
ATOM	1314	OE1	GLN A 181	14.769	57.400	80.176	1.00	17.23
ATOM	1315	NE2	GLN A 181	12.626	57.300	80.812	1.00	12.82
ATOM	1316	N	SER A 182	14.440	55.497	85.821	1.00	20.03
ATOM	1317	CA	SER A 182	14.156	55.600	87.273	1.00	16.56
ATOM	1318	C	SER A 182	14.209	56.973	87.871	1.00	14.78
ATOM	1319	O	SER A 182	13.305	57.369	88.582	1.00	19.49
ATOM	1320	CB	SER A 182	15.056	54.630	88.021	1.00	15.31
ATOM	1321	OG	SER A 182	14.563	53.332	87.714	1.00	16.70
ATOM	1322	N	ARG A 183	15.246	57.738	87.523	1.00	16.99
ATOM	1323	CA	ARG A 183	15.289	59.169	87.858	1.00	15.54
ATOM	1324	C	ARG A 183	14.161	60.085	87.309	1.00	19.55
ATOM	1325	O	ARG A 183	13.693	61.039	87.956	1.00	17.04
ATOM	1326	CB	ARG A 183	16.661	59.785	87.569	1.00	14.08
ATOM	1327	CG	ARG A 183	17.811	59.024	88.265	1.00	19.49
ATOM	1328	CD	ARG A 183	17.716	59.007	89.816	1.00	21.46
ATOM	1329	NE	ARG A 183	18.519	57.930	90.434	1.00	22.16
ATOM	1330	CZ	ARG A 183	19.509	58.121	91.300	1.00	19.15
ATOM	1331	NH1	ARG A 183	19.913	59.335	91.541	1.00	16.50
ATOM	1332	NH2	ARG A 183	20.042	57.081	91.914	1.00	18.34
ATOM	1333	N	VAL A 184	13.681	59.704	86.076	1.00	21.38
ATOM	1334	CA	VAL A 184	12.494	60.417	85.589	1.00	19.02
ATOM	1335	C	VAL A 184	11.194	60.051	86.301	1.00	16.98
ATOM	1336	O	VAL A 184	10.468	60.913	86.800	1.00	18.45
ATOM	1337	CB	VAL A 184	12.368	60.194	84.070	1.00	19.28
ATOM	1338	CG1	VAL A 184	11.057	60.717	83.486	1.00	17.84
ATOM	1339	CG2	VAL A 184	13.517	60.605	83.169	1.00	15.69
ATOM	1340	N	ILE A 185	10.977	58.734	86.408	1.00	17.32
ATOM	1341	CA	ILE A 185	9.834	58.241	87.202	1.00	21.14
ATOM	1342	C	ILE A 185	9.790	58.797	88.672	1.00	22.77
ATOM	1343	O	ILE A 185	8.749	59.230	89.142	1.00	22.95
ATOM	1344	CB	ILE A 185	9.810	56.695	87.193	1.00	20.65
ATOM	1345	CG1	ILE A 185	9.555	56.195	85.758	1.00	18.43
ATOM	1346	CG2	ILE A 185	8.776	56.133	88.202	1.00	18.29
ATOM	1347	CD1	ILE A 185	9.914	54.734	85.494	1.00	14.60
ATOM	1348	N	CYS A 186	10.976	58.837	89.332	1.00	20.34
ATOM	1349	CA	CYS A 186	11.005	59.262	90.745	1.00	21.26
ATOM	1350	C	CYS A 186	10.979	60.766	90.931	1.00	22.80

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ATOM	1351	O	CYS A 186	10.775	61.304	92.009	1.00	23.98
ATOM	1352	CB	CYS A 186	12.220	58.669	91.429	1.00	21.60
ATOM	1353	SG	CYS A 186	12.075	58.576	93.237	1.00	25.16
ATOM	1354	N	GLY A 187	11.149	61.494	89.814	1.00	20.34
ATOM	1355	CA	GLY A 187	11.023	62.949	89.981	1.00	13.75
ATOM	1356	C	GLY A 187	12.351	63.676	90.197	1.00	14.55
ATOM	1357	O	GLY A 187	12.436	64.871	90.453	1.00	16.08
ATOM	1358	N	TYR A 188	13.434	62.894	90.072	1.00	14.86
ATOM	1359	CA	TYR A 188	14.736	63.526	90.226	1.00	16.85
ATOM	1360	C	TYR A 188	15.214	64.366	89.046	1.00	20.24
ATOM	1361	O	TYR A 188	15.979	65.318	89.192	1.00	18.42
ATOM	1362	CB	TYR A 188	15.758	62.441	90.479	1.00	21.64
ATOM	1363	CG	TYR A 188	15.683	61.913	91.899	1.00	27.20
ATOM	1364	CD1	TYR A 188	16.748	62.226	92.737	1.00	32.00
ATOM	1365	CD2	TYR A 188	14.604	61.128	92.365	1.00	30.81
ATOM	1366	CE1	TYR A 188	16.727	61.784	94.071	1.00	35.38
ATOM	1367	CE2	TYR A 188	14.570	60.695	93.705	1.00	30.65
ATOM	1368	CZ	TYR A 188	15.624	61.071	94.556	1.00	35.88
ATOM	1369	OH	TYR A 188	15.607	60.787	95.912	1.00	41.39
ATOM	1370	N	HIS A 189	14.751	63.890	87.862	1.00	19.35
ATOM	1371	CA	HIS A 189	15.215	64.475	86.589	1.00	19.83
ATOM	1372	C	HIS A 189	14.108	64.550	85.551	1.00	16.85
ATOM	1373	O	HIS A 189	13.232	63.689	85.533	1.00	18.10
ATOM	1374	CB	HIS A 189	16.360	63.648	86.032	1.00	15.43
ATOM	1375	CG	HIS A 189	17.677	64.142	86.589	1.00	16.05
ATOM	1376	ND1	HIS A 189	18.154	65.384	86.414	1.00	17.24
ATOM	1377	CD2	HIS A 189	18.581	63.433	87.382	1.00	17.58
ATOM	1378	CE1	HIS A 189	19.347	65.503	87.080	1.00	16.38
ATOM	1379	NE2	HIS A 189	19.587	64.304	87.667	1.00	18.68
ATOM	1380	N	TRP A 190	14.183	65.611	84.723	1.00	18.99
ATOM	1381	CA	TRP A 190	13.341	65.719	83.490	1.00	17.22
ATOM	1382	C	TRP A 190	13.768	64.690	82.453	1.00	15.79
ATOM	1383	O	TRP A 190	14.942	64.354	82.416	1.00	15.77
ATOM	1384	CB	TRP A 190	13.502	67.102	82.855	1.00	16.12
ATOM	1385	CG	TRP A 190	13.134	68.178	83.857	1.00	12.39
ATOM	1386	CD1	TRP A 190	14.033	69.073	84.454	1.00	10.88
ATOM	1387	CD2	TRP A 190	11.800	68.581	84.295	1.00	14.35
ATOM	1388	NE1	TRP A 190	13.343	69.989	85.186	1.00	13.77
ATOM	1389	CE2	TRP A 190	11.976	69.731	85.141	1.00	10.71
ATOM	1390	CE3	TRP A 190	10.505	68.036	84.094	1.00	14.68
ATOM	1391	CZ2	TRP A 190	10.845	70.401	85.666	1.00	12.89
ATOM	1392	CZ3	TRP A 190	9.393	68.700	84.672	1.00	16.93
ATOM	1393	CH2	TRP A 190	9.557	69.875	85.441	1.00	12.82
ATOM	1394	N	GLN A 191	12.859	64.188	81.613	1.00	16.92
ATOM	1395	CA	GLN A 191	13.316	63.234	80.569	1.00	17.49
ATOM	1396	C	GLN A 191	14.519	63.720	79.696	1.00	15.64
ATOM	1397	O	GLN A 191	15.508	63.054	79.429	1.00	16.52
ATOM	1398	CB	GLN A 191	12.113	62.829	79.721	1.00	15.28
ATOM	1399	CG	GLN A 191	12.522	61.832	78.632	1.00	17.26
ATOM	1400	CD	GLN A 191	12.860	60.493	79.206	1.00	16.84
ATOM	1401	OE1	GLN A 191	12.086	59.920	79.946	1.00	21.21
ATOM	1402	NE2	GLN A 191	14.027	59.971	78.864	1.00	16.69
ATOM	1403	N	SER A 192	14.448	65.016	79.389	1.00	17.04
ATOM	1404	CA	SER A 192	15.564	65.622	78.666	1.00	15.81

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ATOM	1405	C	SER A 192	16.899	65.683	79.339	1.00	17.61
ATOM	1406	O	SER A 192	17.937	65.640	78.700	1.00	16.65
ATOM	1407	CB	SER A 192	15.209	67.005	78.211	1.00	15.87
ATOM	1408	OG	SER A 192	14.862	67.833	79.313	1.00	21.12
ATOM	1409	N	ASP A 193	16.886	65.712	80.681	1.00	17.44
ATOM	1410	CA	ASP A 193	18.190	65.648	81.360	1.00	15.23
ATOM	1411	C	ASP A 193	18.889	64.316	81.197	1.00	12.26
ATOM	1412	O	ASP A 193	20.113	64.204	81.054	1.00	14.16
ATOM	1413	CB	ASP A 193	18.036	65.832	82.887	1.00	16.01
ATOM	1414	CG	ASP A 193	17.367	67.116	83.311	1.00	14.57
ATOM	1415	OD1	ASP A 193	17.503	68.180	82.691	1.00	15.89
ATOM	1416	OD2	ASP A 193	16.673	67.038	84.312	1.00	19.14
ATOM	1417	N	VAL A 194	18.025	63.283	81.216	1.00	11.48
ATOM	1418	CA	VAL A 194	18.425	61.882	81.108	1.00	13.18
ATOM	1419	C	VAL A 194	18.851	61.478	79.663	1.00	15.63
ATOM	1420	O	VAL A 194	19.852	60.822	79.387	1.00	15.79
ATOM	1421	CB	VAL A 194	17.210	61.135	81.625	1.00	16.33
ATOM	1422	CG1	VAL A 194	17.152	61.202	83.184	1.00	19.26
ATOM	1423	CG2	VAL A 194	17.079	59.712	81.106	1.00	17.70
ATOM	1424	N	ASP A 195	18.050	61.992	78.728	1.00	16.54
ATOM	1425	CA	ASP A 195	18.488	61.921	77.332	1.00	16.55
ATOM	1426	C	ASP A 195	19.801	62.636	77.029	1.00	14.74
ATOM	1427	O	ASP A 195	20.758	62.076	76.519	1.00	18.92
ATOM	1428	CB	ASP A 195	17.367	62.455	76.477	1.00	15.91
ATOM	1429	CG	ASP A 195	16.139	61.563	76.560	1.00	19.86
ATOM	1430	OD1	ASP A 195	16.153	60.385	76.922	1.00	27.62
ATOM	1431	OD2	ASP A 195	15.090	62.069	76.264	1.00	26.20
ATOM	1432	N	ALA A 196	19.902	63.900	77.450	1.00	15.85
ATOM	1433	CA	ALA A 196	21.203	64.555	77.312	1.00	14.73
ATOM	1434	C	ALA A 196	22.383	63.806	77.932	1.00	18.85
ATOM	1435	O	ALA A 196	23.512	63.751	77.429	1.00	21.06
ATOM	1436	CB	ALA A 196	21.134	65.950	77.904	1.00	13.59
ATOM	1437	N	ALA A 197	22.056	63.177	79.091	1.00	19.14
ATOM	1438	CA	ALA A 197	23.098	62.442	79.808	1.00	17.62
ATOM	1439	C	ALA A 197	23.644	61.202	79.090	1.00	17.71
ATOM	1440	O	ALA A 197	24.851	60.931	79.104	1.00	18.18
ATOM	1441	CB	ALA A 197	22.587	62.002	81.181	1.00	15.91
ATOM	1442	N	ARG A 198	22.711	60.477	78.418	1.00	16.04
ATOM	1443	CA	ARG A 198	23.238	59.409	77.565	1.00	15.41
ATOM	1444	C	ARG A 198	24.179	59.843	76.413	1.00	14.99
ATOM	1445	O	ARG A 198	25.194	59.219	76.113	1.00	17.07
ATOM	1446	CB	ARG A 198	22.136	58.469	77.080	1.00	14.50
ATOM	1447	CG	ARG A 198	21.195	58.043	78.179	1.00	16.67
ATOM	1448	CD	ARG A 198	20.142	57.044	77.730	1.00	19.20
ATOM	1449	NE	ARG A 198	19.280	56.629	78.849	1.00	22.72
ATOM	1450	CZ	ARG A 198	18.003	57.012	79.061	1.00	22.30
ATOM	1451	NH1	ARG A 198	17.412	57.905	78.325	1.00	20.95
ATOM	1452	NH2	ARG A 198	17.292	56.518	80.045	1.00	21.57
ATOM	1453	N	VAL A 199	23.907	61.030	75.842	1.00	17.69
ATOM	1454	CA	VAL A 199	24.961	61.510	74.913	1.00	17.44
ATOM	1455	C	VAL A 199	26.376	61.736	75.457	1.00	18.48
ATOM	1456	O	VAL A 199	27.360	61.145	74.988	1.00	19.25
ATOM	1457	CB	VAL A 199	24.452	62.820	74.284	1.00	15.93
ATOM	1458	CG1	VAL A 199	25.350	63.540	73.279	1.00	11.45

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ATOM	1459	CG2	VAL	A	199	23.072	62.640	73.680	1.00	15.33
ATOM	1460	N	VAL	A	200	26.471	62.548	76.550	1.00	18.52
ATOM	1461	CA	VAL	A	200	27.822	62.723	77.153	1.00	16.27
ATOM	1462	C	VAL	A	200	28.442	61.461	77.794	1.00	14.37
ATOM	1463	O	VAL	A	200	29.643	61.247	77.797	1.00	17.25
ATOM	1464	CB	VAL	A	200	27.811	63.938	78.100	1.00	16.56
ATOM	1465	CG1	VAL	A	200	26.761	63.894	79.246	1.00	13.52
ATOM	1466	CG2	VAL	A	200	27.666	65.177	77.226	1.00	17.14
ATOM	1467	N	GLY	A	201	27.556	60.570	78.283	1.00	14.98
ATOM	1468	CA	GLY	A	201	27.998	59.297	78.836	1.00	13.20
ATOM	1469	C	GLY	A	201	28.609	58.377	77.824	1.00	16.81
ATOM	1470	O	GLY	A	201	29.588	57.701	78.067	1.00	17.03
ATOM	1471	N	SER	A	202	28.034	58.413	76.614	1.00	17.82
ATOM	1472	CA	SER	A	202	28.757	57.750	75.509	1.00	16.70
ATOM	1473	C	SER	A	202	30.087	58.390	75.104	1.00	13.91
ATOM	1474	O	SER	A	202	31.117	57.765	74.939	1.00	18.47
ATOM	1475	CB	SER	A	202	27.813	57.511	74.303	1.00	15.94
ATOM	1476	OG	SER	A	202	27.634	58.737	73.600	1.00	19.26
ATOM	1477	N	ALA	A	203	30.094	59.719	75.030	1.00	14.76
ATOM	1478	CA	ALA	A	203	31.333	60.383	74.641	1.00	14.41
ATOM	1479	C	ALA	A	203	32.527	60.110	75.563	1.00	17.92
ATOM	1480	O	ALA	A	203	33.652	59.803	75.177	1.00	16.36
ATOM	1481	CB	ALA	A	203	31.042	61.872	74.572	1.00	13.61
ATOM	1482	N	VAL	A	204	32.200	60.126	76.880	1.00	18.27
ATOM	1483	CA	VAL	A	204	33.290	59.835	77.823	1.00	16.45
ATOM	1484	C	VAL	A	204	33.834	58.394	77.718	1.00	13.88
ATOM	1485	O	VAL	A	204	35.015	58.177	77.916	1.00	17.64
ATOM	1486	CB	VAL	A	204	32.893	60.245	79.285	1.00	16.63
ATOM	1487	CG1	VAL	A	204	34.131	60.323	80.177	1.00	16.51
ATOM	1488	CG2	VAL	A	204	31.836	59.301	79.862	1.00	13.53
ATOM	1489	N	VAL	A	205	32.971	57.392	77.355	1.00	15.31
ATOM	1490	CA	VAL	A	205	33.648	56.100	77.152	1.00	17.30
ATOM	1491	C	VAL	A	205	34.636	56.018	75.953	1.00	19.20
ATOM	1492	O	VAL	A	205	35.644	55.311	76.002	1.00	19.08
ATOM	1493	CB	VAL	A	205	32.563	55.014	77.035	1.00	19.10
ATOM	1494	CG1	VAL	A	205	32.812	53.549	76.681	1.00	16.51
ATOM	1495	CG2	VAL	A	205	31.797	55.088	78.343	1.00	17.27
ATOM	1496	N	ALA	A	206	34.409	56.893	74.934	1.00	21.03
ATOM	1497	CA	ALA	A	206	35.452	57.018	73.888	1.00	19.17
ATOM	1498	C	ALA	A	206	36.765	57.498	74.469	1.00	19.27
ATOM	1499	O	ALA	A	206	37.809	56.868	74.353	1.00	18.59
ATOM	1500	CB	ALA	A	206	34.982	57.988	72.809	1.00	16.60
ATOM	1501	N	THR	A	207	36.643	58.597	75.234	1.00	20.20
ATOM	1502	CA	THR	A	207	37.873	59.078	75.903	1.00	20.52
ATOM	1503	C	THR	A	207	38.613	58.126	76.838	1.00	21.84
ATOM	1504	O	THR	A	207	39.831	58.030	76.898	1.00	23.45
ATOM	1505	CB	THR	A	207	37.659	60.341	76.674	1.00	19.84
ATOM	1506	OG1	THR	A	207	36.577	61.100	76.137	1.00	20.11
ATOM	1507	CG2	THR	A	207	38.945	61.141	76.710	1.00	21.15
ATOM	1508	N	LEU	A	208	37.806	57.345	77.574	1.00	23.89
ATOM	1509	CA	LEU	A	208	38.323	56.332	78.510	1.00	22.19
ATOM	1510	C	LEU	A	208	39.165	55.285	77.783	1.00	25.28
ATOM	1511	O	LEU	A	208	40.232	54.880	78.228	1.00	24.41
ATOM	1512	CB	LEU	A	208	37.170	55.700	79.312	1.00	21.93

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ATOM	1513	CG	LEU A 208	36.238	56.370	80.325	1.00	24.99
ATOM	1514	CD1	LEU A 208	35.117	55.631	81.058	1.00	26.55
ATOM	1515	CD2	LEU A 208	37.303	56.685	81.377	1.00	22.67
ATOM	1516	N	HIS A 209	38.666	54.873	76.588	1.00	24.64
ATOM	1517	CA	HIS A 209	39.495	53.970	75.766	1.00	20.81
ATOM	1518	C	HIS A 209	40.863	54.530	75.277	1.00	19.15
ATOM	1519	O	HIS A 209	41.807	53.872	74.934	1.00	20.30
ATOM	1520	CB	HIS A 209	38.656	53.449	74.595	1.00	16.87
ATOM	1521	CG	HIS A 209	37.588	52.476	74.994	1.00	13.42
ATOM	1522	ND1	HIS A 209	36.335	52.782	75.375	1.00	14.12
ATOM	1523	CD2	HIS A 209	37.686	51.099	74.975	1.00	12.37
ATOM	1524	CE1	HIS A 209	35.653	51.616	75.586	1.00	10.36
ATOM	1525	NE2	HIS A 209	36.493	50.590	75.334	1.00	13.53
ATOM	1526	N	THR A 210	41.035	55.827	75.336	1.00	20.82
ATOM	1527	CA	THR A 210	42.393	56.384	75.116	1.00	21.40
ATOM	1528	C	THR A 210	43.396	56.387	76.298	1.00	26.34
ATOM	1529	O	THR A 210	44.567	56.745	76.188	1.00	27.83
ATOM	1530	CB	THR A 210	42.315	57.836	74.662	1.00	22.02
ATOM	1531	OG1	THR A 210	42.096	58.723	75.795	1.00	25.04
ATOM	1532	CG2	THR A 210	41.307	58.070	73.528	1.00	20.46
ATOM	1533	N	ASN A 211	42.844	56.032	77.482	1.00	26.32
ATOM	1534	CA	ASN A 211	43.544	56.135	78.782	1.00	23.64
ATOM	1535	C	ASN A 211	44.212	54.824	79.204	1.00	20.62
ATOM	1536	O	ASN A 211	43.591	53.785	79.374	1.00	22.28
ATOM	1537	CB	ASN A 211	42.563	56.749	79.827	1.00	24.99
ATOM	1538	CG	ASN A 211	43.226	56.863	81.206	1.00	24.09
ATOM	1539	OD1	ASN A 211	43.320	55.886	81.935	1.00	25.25
ATOM	1540	ND2	ASN A 211	43.689	58.038	81.566	1.00	21.24
ATOM	1541	N	PRO A 212	45.563	54.884	79.353	1.00	22.01
ATOM	1542	CA	PRO A 212	46.337	53.660	79.633	1.00	21.52
ATOM	1543	C	PRO A 212	45.859	52.883	80.848	1.00	22.52
ATOM	1544	O	PRO A 212	45.670	51.673	80.882	1.00	22.12
ATOM	1545	CB	PRO A 212	47.743	54.190	79.845	1.00	22.52
ATOM	1546	CG	PRO A 212	47.805	55.535	79.117	1.00	25.40
ATOM	1547	CD	PRO A 212	46.391	56.076	79.175	1.00	22.01
ATOM	1548	N	ALA A 213	45.626	53.674	81.897	1.00	23.96
ATOM	1549	CA	ALA A 213	45.139	53.025	83.140	1.00	23.57
ATOM	1550	C	ALA A 213	43.797	52.337	83.019	1.00	21.76
ATOM	1551	O	ALA A 213	43.600	51.185	83.403	1.00	24.96
ATOM	1552	CB	ALA A 213	45.039	54.071	84.259	1.00	21.55
ATOM	1553	N	PHE A 214	42.885	53.085	82.373	1.00	19.30
ATOM	1554	CA	PHE A 214	41.617	52.431	82.017	1.00	20.02
ATOM	1555	C	PHE A 214	41.798	51.170	81.197	1.00	20.38
ATOM	1556	O	PHE A 214	41.255	50.120	81.510	1.00	18.82
ATOM	1557	CB	PHE A 214	40.690	53.445	81.314	1.00	23.58
ATOM	1558	CG	PHE A 214	39.367	52.839	80.840	1.00	26.35
ATOM	1559	CD1	PHE A 214	38.249	52.765	81.711	1.00	24.66
ATOM	1560	CD2	PHE A 214	39.262	52.365	79.507	1.00	23.08
ATOM	1561	CE1	PHE A 214	37.032	52.191	81.265	1.00	27.05
ATOM	1562	CE2	PHE A 214	38.052	51.792	79.077	1.00	19.74
ATOM	1563	CZ	PHE A 214	36.951	51.697	79.944	1.00	22.04
ATOM	1564	N	GLN A 215	42.654	51.298	80.149	1.00	22.02
ATOM	1565	CA	GLN A 215	42.904	50.137	79.275	1.00	21.33
ATOM	1566	C	GLN A 215	43.354	48.889	79.995	1.00	21.73

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ATOM	1567	O	GLN A 215	42.823	47.783	79.875	1.00	21.17
ATOM	1568	CB	GLN A 215	43.970	50.520	78.278	1.00	22.37
ATOM	1569	CG	GLN A 215	43.483	51.517	77.261	1.00	22.30
ATOM	1570	CD	GLN A 215	44.662	52.026	76.479	1.00	28.18
ATOM	1571	OE1	GLN A 215	45.821	51.695	76.664	1.00	32.27
ATOM	1572	NE2	GLN A 215	44.359	52.947	75.605	1.00	28.35
ATOM	1573	N	GLN A 216	44.375	49.154	80.845	1.00	24.60
ATOM	1574	CA	GLN A 216	44.876	48.089	81.718	1.00	25.81
ATOM	1575	C	GLN A 216	43.909	47.530	82.715	1.00	23.07
ATOM	1576	O	GLN A 216	43.822	46.328	82.899	1.00	22.91
ATOM	1577	CB	GLN A 216	46.052	48.544	82.517	1.00	33.78
ATOM	1578	CG	GLN A 216	47.181	49.037	81.631	1.00	49.94
ATOM	1579	CD	GLN A 216	48.161	49.693	82.574	1.00	61.57
ATOM	1580	OE1	GLN A 216	48.354	49.243	83.704	1.00	69.34
ATOM	1581	NE2	GLN A 216	48.737	50.805	82.114	1.00	63.50
ATOM	1582	N	GLN A 217	43.155	48.439	83.377	1.00	22.58
ATOM	1583	CA	GLN A 217	42.099	47.917	84.261	1.00	23.69
ATOM	1584	C	GLN A 217	40.971	47.113	83.590	1.00	24.92
ATOM	1585	O	GLN A 217	40.480	46.102	84.088	1.00	24.09
ATOM	1586	CB	GLN A 217	41.565	49.042	85.189	1.00	23.44
ATOM	1587	CG	GLN A 217	40.720	48.541	86.407	1.00	23.24
ATOM	1588	CD	GLN A 217	41.489	47.589	87.335	1.00	21.58
ATOM	1589	OE1	GLN A 217	42.676	47.749	87.598	1.00	24.82
ATOM	1590	NE2	GLN A 217	40.827	46.516	87.744	1.00	19.85
ATOM	1591	N	LEU A 218	40.628	47.595	82.390	1.00	26.00
ATOM	1592	CA	LEU A 218	39.701	46.859	81.532	1.00	23.47
ATOM	1593	C	LEU A 218	40.195	45.495	81.093	1.00	21.96
ATOM	1594	O	LEU A 218	39.476	44.515	81.209	1.00	22.51
ATOM	1595	CB	LEU A 218	39.309	47.724	80.327	1.00	23.65
ATOM	1596	CG	LEU A 218	38.292	47.073	79.369	1.00	21.04
ATOM	1597	CD1	LEU A 218	38.103	47.980	78.168	1.00	25.30
ATOM	1598	CD2	LEU A 218	36.952	46.736	80.004	1.00	13.22
ATOM	1599	N	GLN A 219	41.451	45.425	80.640	1.00	23.49
ATOM	1600	CA	GLN A 219	42.033	44.079	80.457	1.00	29.37
ATOM	1601	C	GLN A 219	41.880	43.156	81.681	1.00	29.60
ATOM	1602	O	GLN A 219	41.455	42.016	81.569	1.00	29.63
ATOM	1603	CB	GLN A 219	43.544	44.131	80.199	1.00	37.46
ATOM	1604	CG	GLN A 219	44.052	44.703	78.867	1.00	51.74
ATOM	1605	CD	GLN A 219	45.511	45.267	78.911	1.00	60.29
ATOM	1606	OE1	GLN A 219	46.415	44.774	79.568	1.00	65.45
ATOM	1607	NE2	GLN A 219	45.764	46.352	78.161	1.00	60.81
ATOM	1608	N	LYS A 220	42.206	43.722	82.879	1.00	28.28
ATOM	1609	CA	LYS A 220	42.004	42.926	84.111	1.00	26.68
ATOM	1610	C	LYS A 220	40.588	42.446	84.386	1.00	24.54
ATOM	1611	O	LYS A 220	40.347	41.275	84.640	1.00	26.87
ATOM	1612	CB	LYS A 220	42.591	43.631	85.319	1.00	29.93
ATOM	1613	CG	LYS A 220	44.019	43.952	84.934	1.00	36.96
ATOM	1614	CD	LYS A 220	45.015	44.044	86.081	1.00	47.54
ATOM	1615	CE	LYS A 220	44.741	45.121	87.121	1.00	55.28
ATOM	1616	NZ	LYS A 220	44.868	46.456	86.510	1.00	61.92
ATOM	1617	N	ALA A 221	39.630	43.379	84.217	1.00	21.04
ATOM	1618	CA	ALA A 221	38.215	42.960	84.307	1.00	18.69
ATOM	1619	C	ALA A 221	37.761	41.903	83.291	1.00	24.31
ATOM	1620	O	ALA A 221	37.095	40.921	83.598	1.00	26.78



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ATOM	1621	CB	ALA	A	221	37.306	44.177	84.140	1.00	14.85
ATOM	1622	N	LYS	A	222	38.223	42.106	82.029	1.00	24.15
ATOM	1623	CA	LYS	A	222	38.065	41.018	81.046	1.00	23.96
ATOM	1624	C	LYS	A	222	38.668	39.675	81.431	1.00	22.61
ATOM	1625	O	LYS	A	222	38.023	38.628	81.422	1.00	21.88
ATOM	1626	CB	LYS	A	222	38.591	41.444	79.659	1.00	22.92
ATOM	1627	CG	LYS	A	222	37.682	42.516	79.109	1.00	22.76
ATOM	1628	CD	LYS	A	222	38.038	42.903	77.691	1.00	22.50
ATOM	1629	CE	LYS	A	222	37.050	43.918	77.109	1.00	22.07
ATOM	1630	NZ	LYS	A	222	37.556	44.613	75.909	1.00	21.47
ATOM	1631	N	ALA	A	223	39.949	39.728	81.830	1.00	22.84
ATOM	1632	CA	ALA	A	223	40.533	38.472	82.353	1.00	25.17
ATOM	1633	C	ALA	A	223	39.812	37.842	83.543	1.00	26.19
ATOM	1634	O	ALA	A	223	39.534	36.652	83.573	1.00	27.99
ATOM	1635	CB	ALA	A	223	42.013	38.638	82.691	1.00	21.36
ATOM	1636	N	GLU	A	224	39.424	38.696	84.487	1.00	27.72
ATOM	1637	CA	GLU	A	224	38.643	38.187	85.610	1.00	27.59
ATOM	1638	C	GLU	A	224	37.338	37.525	85.191	1.00	28.89
ATOM	1639	O	GLU	A	224	36.971	36.412	85.568	1.00	28.75
ATOM	1640	CB	GLU	A	224	38.476	39.348	86.606	1.00	29.18
ATOM	1641	CG	GLU	A	224	37.470	39.099	87.741	1.00	29.05
ATOM	1642	CD	GLU	A	224	37.335	40.348	88.557	1.00	29.41
ATOM	1643	OE1	GLU	A	224	36.506	41.189	88.269	1.00	28.08
ATOM	1644	OE2	GLU	A	224	38.060	40.487	89.516	1.00	31.14
ATOM	1645	N	PHE	A	225	36.659	38.233	84.288	1.00	29.33
ATOM	1646	CA	PHE	A	225	35.398	37.699	83.770	1.00	28.70
ATOM	1647	C	PHE	A	225	35.551	36.354	83.061	1.00	31.53
ATOM	1648	O	PHE	A	225	34.802	35.399	83.222	1.00	29.17
ATOM	1649	CB	PHE	A	225	34.786	38.756	82.858	1.00	26.48
ATOM	1650	CG	PHE	A	225	33.449	38.281	82.361	1.00	25.90
ATOM	1651	CD1	PHE	A	225	32.361	38.258	83.250	1.00	28.71
ATOM	1652	CD2	PHE	A	225	33.317	37.854	81.022	1.00	28.64
ATOM	1653	CE1	PHE	A	225	31.129	37.758	82.817	1.00	29.98
ATOM	1654	CE2	PHE	A	225	32.074	37.365	80.564	1.00	28.53
ATOM	1655	CZ	PHE	A	225	30.998	37.309	81.479	1.00	30.02
ATOM	1656	N	ALA	A	226	36.635	36.308	82.289	1.00	31.91
ATOM	1657	CA	ALA	A	226	36.996	35.055	81.643	1.00	36.17
ATOM	1658	C	ALA	A	226	37.178	33.829	82.536	1.00	40.94
ATOM	1659	O	ALA	A	226	36.704	32.735	82.271	1.00	41.75
ATOM	1660	CB	ALA	A	226	38.284	35.261	80.877	1.00	33.81
ATOM	1661	N	GLN	A	227	37.883	34.081	83.647	1.00	44.91
ATOM	1662	CA	GLN	A	227	38.067	32.931	84.543	1.00	49.32
ATOM	1663	C	GLN	A	227	36.782	32.579	85.233	1.00	51.62
ATOM	1664	O	GLN	A	227	36.396	31.467	85.528	1.00	50.02
ATOM	1665	CB	GLN	A	227	39.239	33.150	85.499	1.00	50.80
ATOM	1666	CG	GLN	A	227	40.441	33.937	84.900	1.00	59.92
ATOM	1667	CD	GLN	A	227	40.812	33.681	83.397	1.00	68.68
ATOM	1668	OE1	GLN	A	227	40.799	32.592	82.834	1.00	73.97
ATOM	1669	NE2	GLN	A	227	41.221	34.764	82.726	1.00	65.71
ATOM	1670	N	HIS	A	228	36.041	33.669	85.411	1.00	58.91
ATOM	1671	CA	HIS	A	228	34.687	33.501	85.925	1.00	65.53
ATOM	1672	C	HIS	A	228	33.816	32.519	85.143	1.00	68.04
ATOM	1673	O	HIS	A	228	33.014	31.764	85.662	1.00	67.46
ATOM	1674	CB	HIS	A	228	34.091	34.903	86.045	1.00	68.11

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ATOM	1675	CG	HIS	A	228	32.632	34.780	86.283	1.00	71.87
ATOM	1676	ND1	HIS	A	228	31.729	34.968	85.313	1.00	74.51
ATOM	1677	CD2	HIS	A	228	32.007	34.363	87.458	1.00	75.53
ATOM	1678	CE1	HIS	A	228	30.511	34.660	85.852	1.00	78.68
ATOM	1679	NE2	HIS	A	228	30.682	34.288	87.171	1.00	80.02
ATOM	1680	N	GLN	A	229	34.061	32.545	83.846	1.00	74.45
ATOM	1681	CA	GLN	A	229	33.306	31.659	82.963	1.00	81.06
ATOM	1682	C	GLN	A	229	33.569	30.149	83.028	1.00	85.59
ATOM	1683	O	GLN	A	229	33.123	29.427	82.135	1.00	86.52
ATOM	1684	CB	GLN	A	229	33.477	32.181	81.530	1.00	81.47
ATOM	1685	CG	GLN	A	229	33.002	33.631	81.335	1.00	81.55
ATOM	1686	CD	GLN	A	229	31.488	33.690	81.352	1.00	83.81
ATOM	1687	OE1	GLN	A	229	30.804	33.832	82.355	1.00	82.35
ATOM	1688	NE2	GLN	A	229	30.950	33.588	80.141	1.00	86.80
ATOM	1689	N	LYS	A	230	34.317	29.749	84.086	1.00	91.08
ATOM	1690	CA	LYS	A	230	34.965	28.444	84.325	1.00	95.45
ATOM	1691	CB	LYS	A	230	33.976	27.245	84.052	1.00	97.51
ATOM	1692	CG	LYS	A	230	34.256	26.053	83.073	1.00	98.30
ATOM	1693	CD	LYS	A	230	34.035	26.121	81.534	1.00	98.30
ATOM	1694	CE	LYS	A	230	34.810	27.172	80.713	1.00	100.00
ATOM	1695	NZ	LYS	A	230	36.244	27.239	81.067	1.00	100.00
ATOM	1696	C	LYS	A	230	36.409	28.279	83.743	1.00	97.06
ATOM	1697	OCT1	LYS	A	230	36.876	29.108	82.942	1.00	95.86
ATOM	1698	OCT2	LYS	A	230	37.052	27.241	83.957	1.00	99.89
ATOM	1935	S	SO4	S	231	22.561	63.872	89.148	1.00	45.29
ATOM	1936	O1	SO4	S	231	21.748	62.858	88.279	1.00	50.45
ATOM	1937	O2	SO4	S	231	21.648	64.707	90.036	1.00	51.74
ATOM	1938	O3	SO4	S	231	23.551	63.095	90.035	1.00	49.75
ATOM	1939	O4	SO4	S	231	23.260	64.912	88.285	1.00	44.08
ATOM	1	O	HOH	W	232	10.522	63.513	85.670	1.00	17.86
ATOM	2	O	HOH	W	233	34.116	63.633	80.578	1.00	20.45
ATOM	3	O	HOH	W	234	7.928	61.775	88.229	1.00	15.62
ATOM	4	O	HOH	W	235	10.374	64.545	82.597	1.00	14.58
ATOM	5	O	HOH	W	236	15.375	75.641	85.508	1.00	22.07
ATOM	6	O	HOH	W	237	20.773	44.507	86.785	1.00	18.67
ATOM	7	O	HOH	W	238	32.701	49.912	75.935	1.00	15.79
ATOM	8	O	HOH	W	239	21.979	72.096	84.493	1.00	19.08
ATOM	9	O	HOH	W	240	13.158	73.905	82.705	1.00	27.34
ATOM	10	O	HOH	W	241	14.358	71.880	73.410	1.00	26.83
ATOM	11	O	HOH	W	242	5.537	80.043	74.802	1.00	23.33
ATOM	12	O	HOH	W	243	36.136	62.604	78.407	1.00	23.19
ATOM	13	O	HOH	W	244	30.393	53.028	87.579	1.00	19.02
ATOM	14	O	HOH	W	245	28.532	49.107	93.252	1.00	21.32
ATOM	15	O	HOH	W	246	24.657	73.146	75.882	1.00	20.92
ATOM	16	O	HOH	W	247	10.080	55.567	81.848	1.00	33.80
ATOM	17	O	HOH	W	248	29.907	52.840	73.379	1.00	22.59
ATOM	18	O	HOH	W	249	38.583	48.054	74.575	1.00	24.10
ATOM	19	O	HOH	W	250	29.465	68.020	86.676	1.00	32.30
ATOM	20	O	HOH	W	251	12.847	73.680	85.460	1.00	40.76
ATOM	21	O	HOH	W	252	5.516	59.770	95.129	1.00	40.84
ATOM	22	O	HOH	W	253	42.504	47.354	77.319	1.00	30.77
ATOM	23	O	HOH	W	254	13.495	75.378	74.412	1.00	22.57
ATOM	24	O	HOH	W	255	17.100	76.564	77.737	1.00	30.00
ATOM	25	O	HOH	W	256	33.508	40.103	102.712	1.00	26.49

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ATOM	26	O	HOH W 257	20.825	55.648	81.278	1.00	20.11
ATOM	27	O	HOH W 258	19.730	61.701	89.970	1.00	23.10
ATOM	28	O	HOH W 259	4.363	74.520	80.720	1.00	33.74
ATOM	29	O	HOH W 260	31.490	42.656	98.480	1.00	34.19
ATOM	30	O	HOH W 261	6.696	75.130	78.477	1.00	15.66
ATOM	31	O	HOH W 262	10.667	67.023	75.103	1.00	38.86
ATOM	32	O	HOH W 263	8.252	64.433	92.307	1.00	23.15
ATOM	33	O	HOH W 264	41.924	51.223	74.247	1.00	30.19
ATOM	34	O	HOH W 265	1.437	67.705	89.398	1.00	39.48
ATOM	35	O	HOH W 266	4.055	66.946	91.467	1.00	29.22
ATOM	36	O	HOH W 267	3.092	69.112	84.950	1.00	25.58
ATOM	37	O	HOH W 268	9.537	59.065	79.795	1.00	30.90
ATOM	38	O	HOH W 269	9.306	83.197	79.638	1.00	44.19
ATOM	39	O	HOH W 270	34.786	41.166	75.522	1.00	32.98
ATOM	40	O	HOH W 271	28.084	37.193	84.163	1.00	30.43
ATOM	41	O	HOH W 272	40.742	49.227	76.024	1.00	21.82
ATOM	42	O	HOH W 273	35.074	40.712	85.668	1.00	29.87
ATOM	43	O	HOH W 274	30.318	45.526	96.384	1.00	35.57
ATOM	44	O	HOH W 275	31.493	69.162	80.850	1.00	19.51
ATOM	45	O	HOH W 276	42.914	61.700	76.016	1.00	28.69
ATOM	46	O	HOH W 277	34.422	64.714	92.625	1.00	38.81
ATOM	47	O	HOH W 278	13.405	78.374	80.916	1.00	25.22
ATOM	48	O	HOH W 279	44.634	57.811	84.433	1.00	31.73
ATOM	49	O	HOH W 280	44.303	60.992	82.740	1.00	28.14
ATOM	50	O	HOH W 281	32.596	51.432	73.247	1.00	22.63
ATOM	51	O	HOH W 282	22.182	40.126	75.125	1.00	27.50
ATOM	52	O	HOH W 283	18.482	55.362	89.100	1.00	21.25
ATOM	53	O	HOH W 284	36.960	42.360	74.192	1.00	28.88
ATOM	54	O	HOH W 285	35.881	48.845	94.047	1.00	26.90
ATOM	55	O	HOH W 286	26.212	59.698	94.760	1.00	23.37
ATOM	56	O	HOH W 287	29.246	44.303	73.369	1.00	40.38
ATOM	57	O	HOH W 288	27.356	35.947	80.422	1.00	31.74
ATOM	58	O	HOH W 289	40.482	45.029	76.766	1.00	30.88
ATOM	59	O	HOH W 290	24.864	58.724	91.112	1.00	25.30
ATOM	60	O	HOH W 291	28.560	61.547	91.755	1.00	39.37
ATOM	61	O	HOH W 292	27.888	63.113	90.252	1.00	40.28
ATOM	62	O	HOH W 293	31.069	41.023	103.435	1.00	38.13
ATOM	63	O	HOH W 294	5.144	47.860	86.978	1.00	37.63
ATOM	64	O	HOH W 295	29.373	52.425	90.409	1.00	21.69
ATOM	65	O	HOH W 296	41.571	51.401	87.864	1.00	31.72
ATOM	66	O	HOH W 297	35.633	56.807	101.396	1.00	42.27
ATOM	67	O	HOH W 298	35.257	40.157	78.063	1.00	30.17
ATOM	68	O	HOH W 299	33.734	71.189	79.910	1.00	32.64
ATOM	69	O	HOH W 300	17.659	69.593	75.158	1.00	46.73
ATOM	70	O	HOH W 301	17.005	72.932	72.774	1.00	33.93
ATOM	71	O	HOH W 302	15.769	48.059	85.107	1.00	24.21
ATOM	72	O	HOH W 303	15.023	64.697	75.333	1.00	39.99
ATOM	73	O	HOH W 304	13.546	67.305	74.469	1.00	38.11
ATOM	74	O	HOH W 305	30.044	75.863	82.738	1.00	29.02
ATOM	75	O	HOH W 306	5.253	66.383	98.323	1.00	61.09
ATOM	76	O	HOH W 307	25.914	72.829	89.073	1.00	48.08
ATOM	77	O	HOH W 308	38.474	67.620	76.050	1.00	32.88
ATOM	78	O	HOH W 309	34.101	41.534	100.215	1.00	39.54
ATOM	79	O	HOH W 310	29.974	37.419	76.650	1.00	39.99

【図43】

ATOM	80	O	HOH W 311	17.829	44.406	81.773	1.00	29.29
ATOM	81	O	HOH W 312	17.766	66.478	75.705	1.00	34.51
ATOM	82	O	HOH W 313	35.983	70.225	78.152	1.00	38.85
ATOM	83	O	HOH W 314	18.063	58.644	75.592	1.00	33.24
ATOM	84	O	HOH W 315	17.740	45.824	75.692	1.00	31.29
ATOM	85	O	HOH W 316	21.442	55.668	101.498	1.00	30.06
ATOM	86	O	HOH W 317	30.660	37.639	105.501	1.00	46.34
ATOM	87	O	HOH W 318	28.143	47.582	99.410	1.00	71.00
ATOM	88	O	HOH W 319	11.398	65.394	76.821	1.00	34.86
ATOM	89	O	HOH W 320	31.737	45.760	98.744	1.00	38.11
ATOM	90	O	HOH W 321	16.084	45.559	87.137	1.00	43.68
ATOM	91	O	HOH W 322	36.498	37.962	78.989	1.00	35.45
ATOM	92	O	HOH W 323	41.868	42.172	76.980	1.00	56.04
ATOM	93	O	HOH W 324	44.704	68.004	76.606	1.00	73.28
ATOM	94	O	HOH W 325	30.214	44.935	101.119	1.00	28.63
ATOM	95	O	HOH W 326	43.719	69.244	83.004	1.00	32.20
ATOM	96	O	HOH W 327	7.992	54.768	93.490	1.00	36.05
ATOM	97	O	HOH W 328	11.059	49.604	75.476	1.00	43.80
ATOM	98	O	HOH W 329	17.730	37.202	79.516	1.00	44.41
ATOM	99	O	HOH W 330	14.170	59.796	74.913	1.00	70.26
ATOM	100	O	HOH W 331	28.648	70.326	88.645	1.00	34.35
ATOM	101	O	HOH W 332	16.146	57.197	73.492	1.00	49.27
ATOM	102	O	HOH W 333	11.086	52.502	82.116	1.00	39.47
ATOM	103	O	HOH W 334	15.950	60.744	73.392	1.00	63.16
ATOM	104	O	HOH W 335	23.809	74.443	89.142	1.00	63.73
ATOM	105	O	HOH W 336	43.077	70.945	86.543	1.00	41.77
ATOM	106	O	HOH W 337	44.625	68.578	85.466	1.00	42.53
ATOM	107	O	HOH W 338	38.003	70.941	79.707	1.00	47.97
ATOM	108	O	HOH W 339	42.635	39.826	86.317	1.00	39.90
ATOM	109	O	HOH W 340	28.158	51.028	97.893	1.00	35.28
ATOM	110	O	HOH W 341	34.562	57.666	98.193	1.00	56.42
ATOM	111	O	HOH W 342	23.659	34.535	79.197	1.00	84.39
ATOM	112	O	HOH W 343	10.337	58.458	76.704	1.00	45.85
ATOM	113	O	HOH W 344	32.164	75.101	85.461	1.00	54.21
ATOM	114	O	HOH W 345	32.930	38.410	86.586	1.00	43.15
ATOM	115	O	HOH W 346	32.310	36.987	102.558	1.00	47.71
ATOM	116	O	HOH W 347	11.163	49.101	82.634	1.00	84.37
ATOM	117	O	HOH W 348	34.268	69.634	83.019	1.00	47.39
ATOM	118	O	HOH W 349	31.352	37.085	89.579	1.00	74.88
ATOM	119	O	HOH W 350	29.118	56.986	95.860	1.00	34.59
ATOM	120	O	HOH W 351	1.634	70.786	81.659	1.00	41.89
ATOM	121	O	HOH W 352	2.044	71.714	85.736	1.00	37.84
ATOM	122	O	HOH W 353	16.219	75.511	74.471	1.00	44.53
ATOM	123	O	HOH W 354	24.035	45.705	97.204	1.00	48.11
ATOM	124	O	HOH W 355	17.939	77.382	82.853	1.00	65.65
ATOM	125	O	HOH W 356	12.504	76.991	70.634	1.00	50.43
ATOM	126	O	HOH W 357	16.951	78.295	74.889	1.00	47.02
ATOM	127	O	HOH W 358	15.777	75.404	81.566	1.00	33.68
ATOM	128	O	HOH W 359	37.401	72.376	82.831	1.00	50.52
ATOM	129	O	HOH W 360	14.060	44.359	88.918	1.00	80.84
ATOM	130	O	HOH W 361	32.619	76.123	75.757	1.00	42.84
ATOM	131	O	HOH W 362	21.836	66.226	94.339	1.00	63.40
ATOM	132	O	HOH W 363	16.011	46.526	82.837	1.00	38.42
ATOM	133	O	HOH W 364	7.716	57.886	82.470	1.00	50.22

【図44】

ATOM	134	O	HOH W 365	41.813	72.155	81.960	1.00	76.60
ATOM	135	O	HOH W 366	5.810	63.614	94.440	1.00	41.72
ATOM	136	O	HOH W 367	22.833	66.006	98.308	1.00	65.79
ATOM	137	O	HOH W 368	21.384	36.791	76.692	1.00	59.29
ATOM	138	O	HOH W 369	38.765	52.950	92.219	1.00	27.87
ATOM	139	O	HOH W 370	46.430	68.991	81.609	1.00	70.52
ATOM	140	O	HOH W 371	36.973	69.709	83.153	1.00	33.81
ATOM	141	O	HOH W 372	22.238	43.716	92.825	1.00	44.49
ATOM	142	O	HOH W 373	23.096	80.189	77.308	1.00	50.73
ATOM	143	O	HOH W 374	2.790	53.932	81.478	1.00	50.22
ATOM	144	O	HOH W 375	3.292	64.768	94.055	1.00	46.64
ATOM	145	O	HOH W 376	26.937	79.257	75.755	1.00	47.21
ATOM	146	O	HOH W 377	45.046	50.594	85.873	1.00	46.10
ATOM	147	O	HOH W 378	24.988	68.312	90.158	1.00	39.03
ATOM	148	O	HOH W 379	2.045	61.203	93.643	1.00	49.73
ATOM	149	O	HOH W 380	44.273	56.110	87.700	1.00	46.74
ATOM	150	O	HOH W 381	26.747	76.462	73.043	1.00	50.91
ATOM	151	O	HOH W 382	40.545	70.889	76.918	1.00	68.80
ATOM	152	O	HOH W 383	25.523	80.486	83.807	1.00	67.90
ATOM	153	O	HOH W 384	40.972	36.296	87.372	1.00	66.49
ATOM	154	O	HOH W 385	12.617	56.710	77.567	1.00	44.81
ATOM	155	O	HOH W 386	44.460	48.054	74.082	1.00	41.02
ATOM	156	O	HOH W 387	35.781	73.896	86.117	1.00	38.14
ATOM	157	O	HOH W 388	21.625	80.398	81.815	1.00	47.96
ATOM	158	O	HOH W 389	46.628	56.635	82.977	1.00	50.89
ATOM	159	O	HOH W 390	12.308	51.573	78.083	1.00	64.92
ATOM	160	O	HOH W 391	30.773	39.420	87.798	1.00	55.92
ATOM	161	O	HOH W 392	26.088	65.110	89.923	1.00	44.80
ATOM	162	O	HOH W 393	10.719	70.886	96.928	1.00	48.46
ATOM	163	O	HOH W 394	12.474	47.243	84.457	1.00	53.08
ATOM	164	O	HOH W 395	24.296	71.312	91.828	1.00	48.39
ATOM	165	O	HOH W 396	6.459	50.108	83.133	1.00	57.82
ATOM	166	O	HOH W 397	42.423	66.213	75.196	1.00	34.97
ATOM	167	O	HOH W 398	29.045	53.518	101.769	1.00	46.59
ATOM	168	O	HOH W 399	27.195	39.655	105.406	1.00	41.59
ATOM	169	O	HOH W 400	6.834	56.385	96.211	1.00	45.81
ATOM	170	O	HOH W 401	47.957	50.138	78.280	1.00	43.60
ATOM	171	O	HOH W 402	23.330	36.461	72.787	1.00	54.41
ATOM	172	O	HOH W 403	29.051	79.533	81.900	1.00	78.87
ATOM	173	O	HOH W 404	46.670	55.026	74.340	1.00	68.61
ATOM	174	O	HOH W 405	28.985	78.746	85.840	1.00	75.16
ATOM	175	O	HOH W 406	32.117	68.589	73.365	1.00	42.10
ATOM	176	O	HOH W 407	48.677	52.842	75.727	1.00	66.77
ATOM	177	O	HOH W 408	29.185	36.245	72.017	1.00	75.24
ATOM	178	O	HOH W 409	37.168	67.596	97.670	1.00	38.24
ATOM	179	O	HOH W 410	11.986	77.352	92.370	1.00	35.94
ATOM	180	O	HOH W 411	39.548	63.174	98.280	1.00	39.58
ATOM	181	O	HOH W 412	30.500	79.967	79.292	1.00	62.87
ATOM	182	O	HOH W 413	18.003	41.205	83.764	1.00	64.48
ATOM	183	O	HOH W 414	34.455	37.242	89.080	1.00	52.58
ATOM	184	O	HOH W 415	47.074	60.938	83.746	1.00	66.98
ATOM	185	O	HOH W 416	10.880	54.535	78.559	1.00	45.29
ATOM	186	O	HOH W 417	30.230	76.830	74.341	1.00	71.09
ATOM	187	O	HOH W 418	12.118	81.147	79.341	1.00	49.66

【図45】

ATOM	188	O	HOH W 419	32.095	76.945	80.548	1.00	63.23
ATOM	189	O	HOH W 420	-0.301	68.264	84.539	1.00	48.83
ATOM	190	O	HOH W 421	10.822	64.227	102.313	1.00	81.32
ATOM	191	O	HOH W 422	23.374	42.555	101.170	1.00	42.91
ATOM	192	O	HOH W 423	20.016	59.713	74.793	1.00	38.45
ATOM	193	O	HOH W 424	15.833	78.412	79.495	1.00	56.01
ATOM	194	O	HOH W 425	43.534	35.850	84.957	1.00	63.16
ATOM	195	O	HOH W 426	11.933	68.018	98.874	1.00	52.15
ATOM	196	O	HOH W 427	20.777	37.368	85.962	1.00	57.71
ATOM	197	O	HOH W 428	22.392	36.632	89.560	1.00	68.43
ATOM	198	O	HOH W 429	29.340	37.487	101.980	1.00	74.20
ATOM	199	O	HOH W 430	23.237	39.294	91.878	1.00	74.07
ATOM	200	O	HOH W 431	13.654	75.325	94.697	1.00	73.83
ATOM	201	O	HOH W 432	27.904	38.307	96.631	1.00	57.14
ATOM	202	O	HOH W 433	44.213	59.909	79.188	1.00	37.71
ATOM	203	O	HOH W 434	2.129	75.408	79.755	1.00	64.17
ATOM	204	O	HOH W 435	13.993	43.469	84.483	1.00	59.78
ATOM	205	O	HOH W 436	31.644	55.529	99.951	1.00	58.81
ATOM	206	O	HOH W 437	9.462	82.415	76.470	1.00	48.44
ATOM	207	O	HOH W 438	21.813	58.761	98.061	1.00	60.37
ATOM	208	O	HOH W 439	22.202	59.533	93.382	1.00	43.39
ATOM	209	O	HOH W 440	18.118	43.497	86.455	1.00	46.86
ATOM	210	O	HOH W 441	13.762	54.340	105.466	1.00	57.78
ATOM	211	O	HOH W 442	33.277	73.931	83.853	1.00	56.73
ATOM	212	O	HOH W 443	34.442	68.648	90.744	1.00	27.90
ATOM	213	O	HOH W 444	30.640	67.899	91.831	1.00	53.48
ATOM	214	O	HOH W 445	40.813	44.217	74.058	1.00	53.35
ATOM	215	O	HOH W 446	33.012	71.334	90.213	1.00	53.98
ATOM	216	O	HOH W 447	25.130	57.928	101.293	1.00	38.97
ATOM	217	O	HOH W 448	7.584	82.067	74.163	1.00	26.55
ATOM	218	O	HOH W 449	42.214	40.521	78.980	1.00	37.75
ATOM	219	O	HOH W 450	8.915	57.776	101.115	1.00	50.37
ATOM	220	O	HOH W 451	15.963	42.582	79.699	1.00	71.24
ATOM	221	O	HOH W 452	23.011	77.967	75.363	1.00	64.04
ATOM	222	O	HOH W 453	36.910	35.452	88.469	1.00	70.47
ATOM	223	O	HOH W 454	37.814	55.271	99.966	1.00	54.36
ATOM	224	O	HOH W 455	26.721	58.439	99.230	1.00	86.46
ATOM	225	O	HOH W 456	16.108	40.093	81.126	1.00	98.28
ATOM	226	O	HOH W 457	27.800	35.543	96.536	1.00	63.56
ATOM	227	O	HOH W 458	5.859	51.318	95.801	1.00	68.96
ATOM	228	O	HOH W 459	7.841	51.875	96.622	1.00	64.76
ATOM	229	O	HOH W 460	28.280	66.535	89.122	1.00	73.27
ATOM	230	O	HOH W 461	13.943	46.268	81.680	1.00	56.20
ATOM	231	O	HOH W 462	14.681	69.220	73.344	1.00	83.46
ATOM	232	O	HOH W 463	30.388	71.379	89.815	1.00	60.45
ATOM	233	O	HOH W 464	8.062	56.915	75.809	1.00	59.76
ATOM	234	O	HOH W 465	30.104	41.907	101.688	1.00	61.89
ATOM	235	O	HOH W 466	4.988	49.407	95.471	1.00	61.48
ATOM	236	O	HOH W 467	8.747	53.997	77.187	1.00	79.74
END								

【図46】

**A72F(s) 5'-CA-GAC-CTG-GCC-TTT-GGC-GAT-GTG-GC-3'**

**A72F(as) 3'-GT-CTG-GAC-CGG-AAA-CCG-CTA-CAC-CG-5'**

**D L A F72 G D V**

**A72E(s) 5'-CA-GAC-CTG-GCC-GAA-GGC-GAT-GTG-GC-3'**

**A72E(as) 3'-GT-CTG-GAC-CGG-CTT-CCG-CTA-CAC-CG-5'**

**D L A E72 G D V**

【図47】

I103D(s) 5'-TG-ACC-AAT-ATG-GAC-GAG-GAC-GCC-GG-3'  
 I103D(as) 3'-AC-TGG-TTA-TAC-CTG-CTC-CTG-CGG-CC-5'  
 T N M D103 E D A  
 T153N(s) 5'-GG-CAT-ACC-TCT-AAC-GGC-TGG-GCT-AC-3'  
 T153N(as) 3'-CC-GTA-TGG-AGA-TTG-CCG-ACC-CGA-TG-5'  
 H T S N153 G W A

【図48】

L140F(s) 5'-AC-CAG-GAC-AAA-TTC-TCC-AAA-AAT-GG-3'  
 L140F(as) 3'-TG-GTC-CTG-TTT-AAG-AGG-TTT-TTA-CC-5'  
 Q D K F140 S K N  
 L140K(s) 5'-AC-CAG-GAC-AAA-AAA-TCC-AAA-AAT-GG-3'  
 L140K(as) 3'-TG-GTC-CTG-TTT-TTT-AGG-TTT-TTA-CC-5'  
 Q D K K140 S K N  
 L140E(s) 5'-AC-CAG-GAC-AAA-GAA-TCC-AAA-AAT-GG-3'  
 L140E(as) 3'-TG-GTC-CTG-TTT-CTT-AGG-TTT-TTA-CC-5'  
 Q D K E140 S K N

## 【手続補正書】

【提出日】平成12年9月14日(2000.9.14)

## 【手続補正1】

【補正対象書類名】明細書

【補正対象項目名】0050

【補正方法】変更

【補正内容】

【0050】実施例20 エンテロバクター・アエロゲネス IF012010 由来野生型酸性ホスファターゼの精製とN末端アミノ酸配列の決定

特開平10-201481号公報の実施例24記載のエシェリヒア・コリJM109/pENP110の培養菌体からエンテロバクター・アエロゲネスIF012010由来の酸性ホスファターゼを精製してN末端アミノ酸配列を決定し、成熟蛋白質のアミノ酸配列を決定した。エシェリヒア・コリJM109/pENP110はエンテロバクター・アエロゲネスIF012010由来の酸性ホスファターゼ遺伝子をエシェリヒア・コリJM109株に導入した菌で、該酸性ホスファターゼを生産する。該酸性ホスファターゼ遺伝子の塩基配列より予想される前駆体蛋白質のアミノ酸配列は配列表の配列番号10に示される配列に相当する。配列番号10に示すアミノ酸配列は、L61Q/A63Q/E64A/N67D/S69A/G72D/T133K/E134D/I151T変異型EA-APのアミノ酸配列である。ペプトン1g/dl、酵母エキス0.5g/dl及び食塩1g/dlを含有する栄養培地

(pH7.0) 50mlを500ml坂口フラスコに入れ、120℃にて20分間加熱殺菌した。これにエシェリヒア・コリJM109/pENP110を白金耳接種し、30℃で16時間振とう培養した。培養液から遠心分離により菌体を回収した菌体を100mlの100mMリン酸カリウムバッファー(pH7.0)に懸濁し、4℃で20分間超音波処理を行い菌体を破碎した。処理液を遠心分離して不溶性画分を除き、無細胞抽出液を調製した。この無細胞抽出液に30%飽和となるように硫酸アンモニウムを添加した。遠心分離により生成した沈殿を除去した後、上清液に60%飽和となるように硫酸アンモニウムを追加添加した。生成した沈殿を遠心分離により回収し、100mMリン酸カリウムバッファーに溶解した。この粗酵素液を100mMリン酸カリウムバッファー(pH7.0) 500mlに対し3回透析した後、20mMリン酸カリウムバッファー(pH7.0)で平衡化したDEAE-トヨパール650Mカラム(φ3.0×10.0cm)にチャージし、20mMリン酸カリウムバッファー(pH7.0)で洗浄した。リン酸転移活性は素通り画分にあつたので、当該画分を回収した。この活性画分に35%飽和となるように硫酸アンモニウムを添加し、これを35%飽和硫酸アンモニウムを含む20mMリン酸カリウムバッファー(pH7.0)で平衡化したブチルトヨパールカラム(φ3.0×7.0cm)に吸着させた。これを35%飽和から20%飽和リン酸カリウムバッファー(pH7.0)の直線的な濃度勾配で溶出した。活性画

分を集め、10mMリン酸カリウムバッファー (pH6.0) 1 L に対し透析した後、10mMリン酸カリウムバッファー (pH6.0) で平衡化したCM-トヨパール カラム (φ3.0×7.0cm) に吸着させた。これを0mMから300mM 塩化カリウムを含むリン酸カリウムバッファー (pH6.0) の直線的な濃度勾配で溶出した。この活性画分を集めた。以上の操作によって、リン酸転移活性を示す酵素を無細胞抽出液より最終的に約16%の回収率で約5倍に精製した。この酵素標品は、SDS-ポリアクリルアミド電気泳動において均一であった。本精製酵素をDITC メンブレン [ミリゲン/バイオサーチ (Milligen/Bioscience) 社製] に吸着させ、Prosequencer 6625 (ミリゲン/バイオサーチ社製) を用いてN末端のアミノ酸配列を決定したところ配列表の配列番号98に示した5残基のN末端のアミノ酸配列が決定された。精製酵素のN末端は配列表の配列番号10の配列の21番目のアラニン残基から開始していたため、配列表の配列番号10に示されるアミノ酸配列は前駆体蛋白質の配列であり、1番目のメチオニン残基から20番目のフェニルアラニン残基までのペプチドは翻訳後に除去されるものと考えられた。この結果より成熟体蛋白質のアミノ酸配列は配列表の配列番号10に示される配列中、アミノ酸番号1～228に示される配列に相当する。

【手続補正2】

【補正対象書類名】明細書

【補正対象項目名】0062

【補正方法】変更

【補正内容】

【0062】実施例23 グアノシンに対する親和性の向上したエンテロバクター・アエロゲネス IF0 12010 由来新規変異型酸性ホスファターゼ遺伝子導入菌によるグアノシンのリン酸化反応  
それぞれの変異型酸性ホスファターゼ遺伝子を含むプラスミドを導入したエシェリヒア・コリ JM109/pENP180、エシェリヒア・コリ JM109/pENP320、エシェリヒア・コリ JM109/pENP340、エシェリヒア・コリ JM109/pENP410、エシェリヒア・コリ JM109/pENP510、及びエシェリヒア・コリ JM109/pENP520をアンピシリン 100 µg/ml 及び IPTG 1mM を含む L 培地 50ml に接種し、37℃で16時間培養した。ピロリン酸 10g/dl、及び特願平12-189226号明細書の実施例1と同様に調製した粉碎グアノシン 6.6g/dl を 100mM 酢酸バッファー (pH4.5) に溶解し、これにそれぞれの菌体を乾燥菌体重量で 100mg/dl となるように添加し、pH を 4.5 に維持しながら、35℃で12時間反応させた。生成した5'-グアニル酸の量を表17に示した。表17に示すように変異型酵素を導入した菌はいずれも親株であるエシェリヒア・コリ JM109/pENP180に比べて生産性が向上し、高い収率で5'-グアニル酸を生成蓄積した。

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